SEPTEMBER, 1953

TEXAS State Journal of Medicine

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VOLUME 49 • NUMBER 9 • AUSTIN, TEXAS

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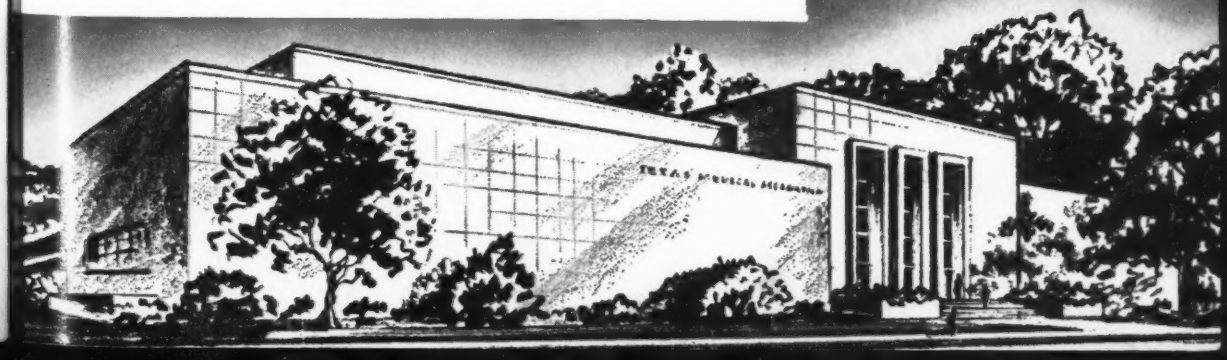

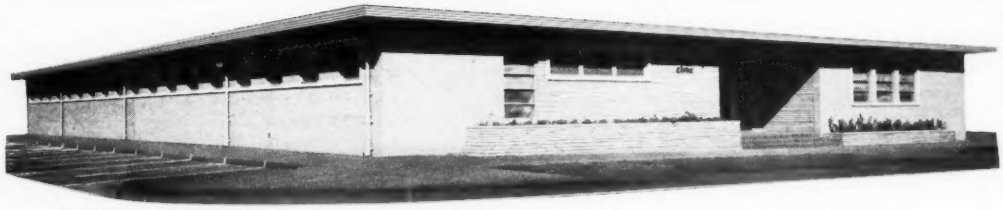

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Texas State Jouurnal of Medicine is published monthly by the Texas Medical Association. Subscription price, $3.00 yearly, 50 cents per copy. Entered as Second Class Matter July 1, 1905, at the Post Office at Fort Worth, Texas, under act of March 3, 1879.
Address all communications to Texas Medical Association, 1801 Lamar Blvd., Austin, Texas

President's Page

ORGANIZED MEDICINE AT THE COUNTY, DISTRICT, AND STATE LEVELS

In many respects the county medical society is the most important component of organized medicine. Ideas concerning accepted principles of medical practice originating here are more effective than mandates handed down from above. It is here also that a physician is judged by his fellows with regard to the pattern of conduct he follows in practice and his educational attainments. If his professional conduct does not conform to accepted principles of medical ethics or if the quality of instruction he has received is not acceptable, he cannot become a member. Without being a member he is barred from staff membership in approved hospitals and denied participation in scientific programs and many local society activities affecting the welfare of the physician and the community. There are approximately 600 doctors in Texas who do not belong to a county society. More than this number belong but do not regularly attend meetings or actively participate.

The constitution and by-laws of all county medical societies in Texas conform to the Constitution and By-Laws of the State Association. Consequently, the county society functions to make effective and operative in the community the program of policies and activities determined upon through deliberation in the House of Delegates of the State Association. This program is dependent upon how well it is interpreted by the county societies through their officers and committees. The Conference of County Medical Society Presidents and Secretaries held each year in January achieves much toward the expansion of local society effort and accomplishments.

The county medical society is the medium of expression of medical opinion locally, and the Texas Medical Association and the American Medical Association at state and national levels. To come to a full realization that our county societies are most important and make them leaders in their communities in all health matters, attendance is the major factor. The busy day-by-day basis on which most physicians

work at their task of overcoming disease and making people well causes them too often to lose sight of the united strength in their county society. The physician's first personal obligation is to himself and his patient. His first medical organization obligation is active participation in his local society. All matters concerning or affecting the practice of medicine should transpire before the county society meetings. Each member has a voice if he is only present to speak it. If the newest member in a county society conceives a worthy principle affecting the practice of medicine or its organization, he is at liberty and invited to introduce a resolution setting forth his idea. In case his resolution is adopted, the delegation from his society will be instructed to introduce it in the House of Delegates of the State Association. Provided that the resolution is approved, delegates will be instructed to introduce it in the House of Delegates of the American Medical Association. If acted upon favorably, the resolution becomes an accepted part of the principles and methods employed in the practice of medicine in America. No organization could be more democratic.

The Texas Medical Association is the organization thought by the public as representing organized medicine and what it stands for in the state. Many times there is a belief that it operates as a closed corporation for the sole pecuniary benefit of its members. Nothing could be further from the truth. Our public relations must continue to educate both the profession and the public as to the facts concerning the objectives and purpose of this Association. The State Association exists to unify and co-ordinate the district and county societies. The district and county societies exist to unify and co-ordinate the efforts of the individual doctors in the locale where they practice. This is the mud sill of the whole set-up where scientific medicine is practiced. The responsibility is on the individual doctor. Each might ask himself, "What kind of a medical society will this be, if every member is just like me?"

George Tilney M.D.

PR diagnotes

REPORT OF PUBLIC RELATIONS COMMITTEE: Special sections deadlines drawing near for some fifteen county medical societies and cooperating newspapers. Prospects for overwhelming success of issues good--societies enthusiastic. Look for sections commemorating "100 Years of Medicine in Texas" in Houston, Dallas, Fort Worth, San Antonio, Austin, El Paso, Corpus Christi, San Angelo, Wichita Falls, Jacksonville, Big Spring - others may be forthcoming.

September 10 "Medical Students Day" in Dallas very successful. With approximately 350 future doctors in attendance, program presented covered practical aspects of future practice seldom found in medical books. Held in cooperation with Dallas County Medical Society, Texas Medical Association participated. All attending felt first step in future intraprofessional relations with undergraduates was well taken. Dallas Society stands congratulated for its part in planning and execution. Southwestern Medical School, Dallas - also, thanks.

"PR Activities Outline Guide for County Medical Societies" out last month. Societies have probably received them at this writing. Those who are not in receipt should write Association headquarters. Central offices have mailed complete "Medical Forums" story to county societies. Public Relations Committee felt this brochure published by the St. Petersburg, Fla., Times in cooperation with the Pinellas County Society to be an excellent fact-information item by "Medical Forum" originators. Brochure covers history, staging, and results of two years' forums. These forums have become one of the most discussed subjects in medical public relations field today. Committee remains highly in favor of county societies staging such, if practical in your area.

"Better Secretaries-Training Tips" response still surprising. Association headquarters reports over 1,800 orders filled to date. Definite course outlines should be ready by the time of this reading.

Special Committee on Doctor Distribution on the move. Test survey being held in District 7 currently. Purpose of test is to gauge response from communities in order to set up mechanics for statewide program. Program should go far in disproving unfounded rumors of inadequate

doctor supply in selected areas as well as improve community-profession relations in those areas where shortage actually exists.

Association's public relations counsel, W. E. Syers, on hand at AMA Public Relations Clinic, Drake Hotel, Chicago, September 2-3. Reason was invitation to participate on official program. Mr. Syers spoke on "Publicizing a State Association Meeting"; also handled panel discussion.

ON THE NATIONAL SCENE: Interested parties can get copies of recent statement of the American Medical Association made by Dr. Walter B. Martin of Norfolk, Va., to the Subcommittee on Hospitals of the Committee on Veterans' Affairs of the House of Representatives. Place - Texas Medical Association headquarters. Excellent material on hospitalization of veterans with non-service-connected disabilities. Another fine fact-roundup of present legislative situation in AMA Special Report 9, dated July 29 - also at your own headquarters on Lamar, Austin.

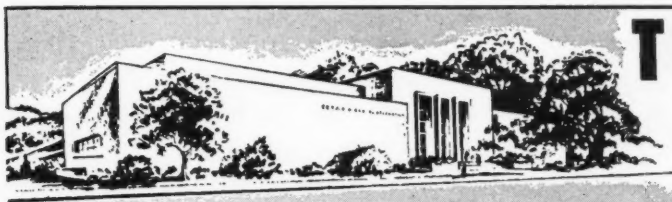
AMA Washington Letter 31 reports Dr. Chester Scott Keefer's appointment to the post of Special Assistant (Health and Medical Affairs) to the Secretary of Health, Education, and Welfare under Mrs. Hobby. Dr. Keefer is professor of medicine at Boston University School of Medicine, graduate of Johns Hopkins University, 1922, fellow of the American College of Physicians, member of the American Society of Clinical Investigation, and former member of the American Medical Association's Council on Pharmacy and Chemistry.

OTHER STATES REPORT: Medical Society of the State of North Carolina is conducting an industrial survey regarding existing medical facilities in plants. Survey is designed to obtain information which may serve as a basis for some joint health and protection services to workers through private enterprise resources. Survey is being handled by a Committee on Occupational Health.

FROM OVER THE STATE: Woman's Auxiliary to the Texas Medical Association busy on many projects this month - among them, purchasing films for use by local auxiliaries. An outstanding film on Nurse Recruitment recently purchased - called "Keepers of the Lamp." Several films were to be reviewed prior to September 10 Auxiliary Executive Board meeting in Austin.

Association's Memorial Library, Austin, cleaning out the files, buying up-to-date films. Special emphasis is being given to furnishing film as well as information for speaker's tie-in. Excellent service.

Harris County Medical Society reports kick-off of AMEF fund drive. Team captains and lieutenants lined up. Special dinner for explanations and publicity peg scheduled. Woman's Auxiliary being used to advantage, too. Campaigns should be under way all over the state by now.



TEXAS State Journal of Medicine

DEVOTED TO THE INTERESTS OF THE MEDICAL PROFESSION AND PUBLIC HEALTH IN TEXAS

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Volume 49 **Austin, Texas, September, 1953** **Number 9**

RESPONSIBILITY IN RECRUITMENT OF MEDICAL PERSONNEL

The need for more qualified professional and technical personnel in fields ancillary to medicine has been brought to the fore oftentimes in recent years, and in many instances, steps have been taken to recruit more medical workers. Even so, most authorities agree that serious personnel shortages still exist, for although it is true that today's number of medical workers far exceeds that of two or three decades ago, it is also true that demands for their services have increased with each new advance in medical knowledge.

Particular emphasis has been placed on the necessity of procuring more nurses and medical technologists. It is estimated that the present demand for graduate nurses exceeds the supply by more than 50,000. In outlining some current medical problems as goals of achievement for 1953-1954, Dr. George Turner, President of the Texas Medical Association, recognized the need for more nursing care and stated: "The nursing service supply has not kept up with the demands by increased population, more people going to hospitals, shorter hospital stays per patient, needs of the armed services, extension of public health services, and needs of industrial care." Dr. Turner pointed out that in Texas plans are under way to initiate an educational program whereby more young people may be persuaded to become vocational and graduate nurses.

The Woman's Auxiliary to the Texas Medical Association has taken part in nurse recruitment programs for several years, and the results of its work have been gratifying. Through such means as the creation of scholarships and loan funds, dissemination of educational material, establishment of future nurses clubs, cooperation with other interested groups, and participation in vocational guidance work, definite progress in nurse recruitment has been made.

A nationwide recruitment program directed at enlisting more people as medical technologists will be launched soon by the American Society of Clinical Pathologists. This group reports that there are approximately 70,000 potential positions available for qualified tech-

nologists, as compared to the 18,021 technologists presently registered.

In the past, those who thought of pursuing a career in medicine envisaged only the possibilities of becoming physicians, dentists, nurses, or pharmacists. That limited concept of the structure of the medical care team still exists to a large degree. Many young people are uninformed of the work being done by such groups as medical technologists, x-ray technicians, dietitians, physical therapists, occupational therapists, medical social workers, and medical record librarians. This lack of information coupled with the heavy demands being made by industry, the armed services, and other professions for the same qualified young people as those needed in medicine are two major factors in the personnel shortage problem.

The role medical workers play in helping physicians to provide improved medical care for more patients is an important and necessary one. Their efforts greatly augment the "output per physician," for in this day of continuously increasing medical knowledge and medical facilities, it would be impractical and almost impossible for each individual physician to perform personally the multitude of tasks delegated to nonphysician medical personnel.

Each physician and Auxiliary member should assume a responsibility for acquainting young people with the wide range of work and opportunities open to them in fields allied with medicine. The same techniques which are being used to recruit prospective nurses and medical technologists could be applied to alleviating existing personnel shortages in other realms of medical work.

VACATION VERSUS VOCATION

An Arizona banker-economist named H. A. Leggett describes a vacation as "a chaotic interlude of voluntary frustration sandwiched in between six months of anticipation and six weeks of recuperation." He goes on to point out that a vacation encourages us to "sleep too much or too little, eat too much or too little, exercise too much or too little and, in general, comport ourselves in a manner calculated to do more physical damage in a few days than can ever be repaired short of a sanitarium, or another vacation."*

It is to be hoped that Texas physicians this summer have been more temperate in their vacation activities than Mr. Leggett's typical escapee from the office clock and will manage to return to their practices refreshed in body and spirit. But what then?

Time after time statistics have proved relentlessly that doctors, who should know better, drive themselves too hard and become subject to the very ills which they decry in their patients. There is a reason why coronary occlusion is called the "doctor's disease."

Why not resolve to make the beneficial effects of the 1953 vacation last longer by easing up a bit, getting a little more sleep, playing with the youngsters more often, and taking the wife out to dinner occasionally in the months before the next annual vacation rolls around? Certainly no one wants the patients to be neglected, but most patients prefer a doctor who is relaxed, rested, and ready for whatever comes.

*Saturday Review, August 1, 1953, p. 5.

FROM THE HEART—AND MORE

"Give from the heart" has been a catchword for fund-raising campaigns in the past.

Today to this admonition something more needs to be added—"Know to what you are giving." With so many organizations vying for a share of the philanthropy dollar, it becomes not so much a matter of wanting to give as it is of deciding how to spend the part of the personal budget set aside for such purposes.

For individual drives the task is not so hard: The aims of cancer, heart disease, poliomyelitis, and other similar campaigns are self-evident.

However, in a concerted community drive, such as those which many cities will hold this fall, it is not always so easy to know what groups benefit. Monies collected in this manner are distributed to more than 18,000 services. Each of the 1,700 cities and towns in the United States, Canada, the Philippines, the Canal Zone, Japan, South Africa, and Australia which participates in a plan of this kind sets its own goal, decides what agencies to include in its federation, and budgets the funds for all.

A National Information Bureau helps to screen out for local chambers of commerce, better business bureaus, or community chests the projects that have not proved effective and worth while; out-and-out "charity rackets" and frivolous projects are excluded. Even so, budgets of agencies in community campaigns are open to the public, and someone contemplating giving to such a fund is not only invited but urged to make his own investigation.

Physicians will be particularly interested in seeing what health organizations are included in their local drives and will want to let others know so that health agencies do not lose their identity. If certain groups in which the individual doctor is interested are not represented, he will want to support them with additional donations.

There are advantages to concerted fund raising campaigns: the reducing of administrative costs involved in separate drives, the raising of more money in the aggregate, the saving of time and energy of volunteer workers, as well as elimination of the nuisance of separate appeals to the contributor. On the other hand, certain organizations believe that citizens prefer giving to specific projects with pinpointed objectives and wish to utilize individual campaigns for educational as well as fund raising purposes.

Fortunately, America is still a land of free choice, and no one method of fund raising—individual or collective—is compulsory upon a given community. Regardless of what method his community has chosen, the conscientious citizen will wish to do his share of giving. In so doing, however, he will want to be well posted as to what he is giving.

It becomes important, therefore, not only to "give from the heart" but also to "give with an enlightened mind."

DERMATOLOGY ESSAY CONTEST

Cash prizes of $500, $300, and $200 will be awarded by the American Dermatological Association for essays based on original work, not previously published, relative to some fundamental aspect of dermatology or syphilology. Competition is open to scientists generally, not only to physicians, and the deadline for submitting the essays in triplicate to Dr. J. Lamar Callaway, secretary, American Dermatological Association, Duke Hospital, Durham, N. C., is December 1. Results are to be announced before January 1.

In addition to the cash prize, the first place winner may be asked to present his paper before the association's annual meeting in April, 1954, at White Sulphur Springs, W. Va., with expenses paid.

STATE MEETING ON SERVICES TO AGED

A statewide meeting on community services to the aged was held in Austin August 4-5 under the sponsorship of the Travis County Nursing Association, the Austin-Travis County Mental Health Society, and the Tarrant County Nursing Home Operators Association. Keynote address was given by Canon Edward B. Ferguson, director of the E. D. Farmer Foundation, Dallas.

Individual discussion groups met to discuss such topics as nursing care for the aged, professional standards in nursing homes, local coordination of health and welfare facilities, recreation for older people, religious services to the aged, legislation, research in later maturity, community services, and changing attitudes for old age care. These groups reported to a panel, which was moderated by Dr. Carl F. Hereford of the Austin Community Guidance Center.

On the second day of the meeting, a panel discussion was held on "Coordination of Community Facilities for Services to the Aged" following the showing of a movie, "Retire to Life." Herbert C. Wilson of the State Department of Public Welfare was moderator for the panel discussion.

Talks were also given on nursing home problems, care of nursing home residents, and nursing homes in relation to the health department and to fire protection. Luncheons and coffees were also planned.

Essay Competition on Cardiac Surgery

"Recent Advances in Cardiac Surgery" is the topic for the essay competition for the Caleb Fiske Prize of the Rhode Island Medical Society. A cash prize of $250 is offered. Information concerning regulations is available from the secretary, Caleb Fiske Fund, Rhode Island Medical Society, 106 Francis Street, Providence 3, R. I.

ORIGINAL ARTICLES

CLINICAL USE OF PARA-AMINOBENZOIC ACID

CHRIS J. D. ZARAFONETIS,* M.D., F.A.C.P., Philadelphia, Pennsylvania

ALTHOUGH para-aminobenzoic acid (PABA) was first synthesized in 1863, its biologic importance has become recognized only recently. Indeed, it was not until 1940 that its role as an essential metabolite was discovered. At that time, Woods noted the antagonism between PABA and sulfanilamide, and his observations concerning the relationship of these compounds provided a great stimulus to further study of the concept of "metabolite antagonism" for structurally similar chemicals.

PABA is now generally considered to be a member of the B-complex group of vitamins and is a known constituent of many food substances. It is of interest, however, that there has been described no clinical syndrome in man which can be attributed to a deficiency of this substance. To date, therefore, PABA has been employed in massive doses as a chemotherapeutic agent rather than as a vitamin. In this connection, it may be recalled that the first major clinical use of PABA was for the treatment of epidemic typhus fever and other rickettsial diseases during World War II. It seems especially appropriate to cite the early contributions on the use of PABA in murine typhus by Levy and Arnold,[5] and in experimental Rocky Mountain spotted fever by Anigstein and Bader.[1] The newer broad spectrum antibiotics, of course, have largely supplanted the use of PABA in the treatment of rickettsial diseases. More recently, however, additional studies have yielded encouraging results in a number of diverse conditions of unknown etiology. These include chronic granulocytic leukemia,[13, 19] lymphoblastoma cutis,[16] certain forms of lupus erythematosus,[9, 14] dermatomyositis,[15] scleroderma,[4, 12, 13, 15] periarteritis nodosa,[8] rheumatoid arthritis,[21] dermatitis herpetiformis,[20] pemphigus,[17] hydroa vacciniforme,[18] and eczema dermatitis and atopic dermatitis.[6, 11]

In the present discussion, some of the results achieved with PABA in dermatomyositis, scleroderma, and rheumatoid arthritis will be described briefly. The serious systemic nature and the widely different manifestations of these disorders influenced their selection for presentation at this time.

Read before the Section on Internal Medicine, Texas Medical Association, Annual Session, Houston, April 29, 1953.

**Associate Professor, Department of Internal Medicine, Temple University School of Medicine.*

For administration to patients, it has been found that PABA is best tolerated as a neutral salt. Crystalline PABA is less soluble and gives rise to gastrointestinal disturbance through mucosal irritation. In my experience, the potassium salt (KPAB)* is preferable to the sodium salt as the former does not contribute to the development of edema. Furthermore, KPAB is less frequently associated with anorexia and nausea. Like other potassium salts, however, KPAB is best given in liquid form. Patients generally prefer a 10 per cent aqueous solution of KPAB to taking the equivalent amount in capsules or tablets. Solutions of PABA salts will darken upon exposure to ultraviolet light, so that they should be kept in a dark place, preferably refrigerated.

Since KPAB is rapidly excreted in the urine, it is necessary to administer repeated doses at approximately three hour intervals to achieve optimal therapeutic effectiveness. For example, patients receiving 12 Gm. daily would take 6 doses of 20 cc. each of the 10 per cent solution. It has been found convenient to schedule doses at breakfast, midmorning, lunch, midafternoon, dinner, and bedtime.

Hypoglycemia, which will be referred to again, may be prevented by instructing the patient to maintain an adequate diet. Should anorexia or nausea occur, the administration of KPAB should be interrupted until the patient is again eating well.

The amount of KPAB required for effective results varies according to the disorder being treated. After much trial, the following tentative treatment schedules have been evolved: For scleroderma and rheumatoid arthritis 12 Gm. daily (6 doses of 2 Gm. each); in addition, patients with rheumatoid arthritis are given 2.4 Gm. of acetylsalicylic acid, in 4 doses of 0.6 Gm. each. In some instances, the amount of aspirin has been even less. Adults with dermatomyositis receive 18 Gm. daily (6 doses of 3 Gm. each). Although these dosage schedules are employed initially for the respective diseases, treatment may be modified in individual patients. Aside from appropriate dosage, however, the most important requirement of KPAB therapy in these conditions is that of prolonged administration. This and other aspects

**The potassium para-aminobenzoate used in this study was generously supplied by the Glenwood Laboratories, Teaneck, N. J., and by Wyeth and Co., Philadelphia.*

of KPAB treatment will be evident from the illustrative case histories which will be presented later.

DERMATOMYOSITIS

The use of potassium para-aminobenzoate in dermatomyositis stemmed directly from the studies of its effects in lupus erythematosus.[14] Extensive trials in the latter disorder have shown para-aminobenzoic acid to exert beneficial effects in discoid lupus erythematosus and even in patients with subacute forms of the disease. By itself, however, KPAB is inadequate for the treatment of acute disseminated lupus erythematosus. Since it is the latter clinical form of the disease which confronts the internist, the effect of KPAB in milder forms of lupus erythematosus will not be reiterated here. Rather, mention of this aspect of KPAB therapy has been made since the rationale for administration of KPAB to patients with dermatomyositis was based on the prior observations made in another so-called "collagen disease."

So far, I have treated 9 cases of dermatomyositis or dermatomyositis with mixed features of other collagen disorders. Two of these cases were documented in an earlier report.[15] In table 1 are summarized the

TABLE 1.—*Results of Potassium Para-Aminobenzoate Therapy in 9 Cases of Dermatomyositis.*

Diagnosis	Results				Total
	None	Slight	Moderate	Marked	
Dermatomyositis	1*	1†		4	6
Sclerodermatomyositis			1‡	1	2
Poikilodermatomyositis				1‡	1
Total	1	1	1	6	9

*Fulminating course; death possibly delayed but not prevented by therapy.
†Child, aged 3, died of bronchopneumonia while on therapy.
‡Treatment continuing at time of evaluation. Remaining patients in complete remission.

results in all 9 cases treated.* Four of these patients were treated for periods of from nine to twelve months and their diseases have remained in remission since the KPAB was stopped two and one-half to three and one-half years ago. A patient with poikilodermatomyositis has shown marked clinical improvement and has been on KPAB therapy, 12 Gm. daily, for more than three years. This patient has extensive generalized muscular calcinosis, and it is hoped that continued suppression of the inflammatory process will enable resorption of at least some of the calcium deposits.

The following case report depicts a patient with dermatomyositis and her response to KPAB therapy. It also describes an associated malignancy which underscores the remarkable predisposition to the development of neoplasms exhibited by many patients with this disease.

CASE 1.—M. O., a 55 year old white woman, was admitted to the Temple University Hospital on February 5, 1952, complaining of a skin rash and profound muscular weakness. She dated her illness back one year when she weighed 230 pounds and began taking "reducing pills." In June, 1951, following short exposure to sunlight, she developed erythema of the face, the V of the neck, breasts, forearms, and thighs. After unsuccessful treatment with various ointments and local applications, the patient consulted a dermatologist, Dr. Carrol S. Wright, on July 12. At that time she presented an eruption limited to the exposed surfaces of her body. It was characterized as a generalized blotching and bright red erythema which faded on pressure. There was some lichenification, but no vesicles or bullae were seen. The clinical impression was "an extensive lichenoid eruption, suggesting acute lichen rubrum planus with a secondary diagnosis of lupus erythematosus." Treatment consisted of small doses of Bistrimate internally for six weeks, bland diet, simple lotions, and local roentgen-ray therapy to the front and sides of the neck.

On September 6 she complained of weakness, easy fatigability, and vague aching of the shoulders. She was hospitalized for further studies on September 10. A skin biopsy was reported as showing "mild dermatitis." The fasting blood sugar level was 180 mg. per 100 cc. An intravenous glucose tolerance test was performed, and the blood glucose was 268 mg. per 100 cc. one hour after the injection and 203 mg. per 100 cc. at the third hour of the test.

Following discharge from the hospital the patient developed diffuse alopecia and noted increasing muscular weakness. Getting in and out of bed and climbing stairs became difficult. The shoulder girdle showed atrophy, and she could hold only light objects because of weakness. Periorbital swelling also was present intermittently. The diagnosis of dermatomyositis was considered at this time, but steroid therapy was believed contraindicated in view of the diabetic glucose tolerance curve. The patient therefore was referred for further study and possible KPAB therapy.

Physical examination revealed the patient to be in no acute distress. The admission weight was 158 pounds. The blood pressure was 154/92, right arm recumbent. The skin of the forearms and dorsa of the hands, and of the thighs and lower half of the abdomen was dusky red with thickening and fine desquamation. There was patchy involvement of the base of the neck, the breasts, arms, and lower legs. There was marked thinning of the hair. Wasting of the muscles of the shoulder girdle, arms, forearms, and flexors of the thighs was noted. The arms could be abducted only about 30 degrees (fig. 1a). The patient was unable to sit up or roll over in bed, or to raise her hands to the top of her head. The remainder of the physical examination was noncontributory.

TABLE 2.—*Twenty-Four Hour Urinary Creatine Excretions in a 55 Year Old White Woman with Dermatomyositis During Treatment with Para-Aminobenzoic Acid.*

Date	Day of PABA Treatment	Creatine (mg.)
2/ 7/52	0	361
2/12/52	4	102
3/ 6/52	27	95
2/23/53	—	0

Laboratory studies revealed the hemoglobin, erythrocyte, and leukocyte values to be within normal limits. A lupus erythematosus cell preparation was negative. The admission

**In addition to these patients, Dr. R. Pommerening of Seattle, Wash., in a personal communication reports a patient with typical findings of dermatomyositis who experienced "rather prompt and amazing results on PABA." Dr. William Shull of Charlotte, N. C., also has achieved gratifying results in a patient with dermatomyositis.*

urinalysis showed a faint trace of albumin, but was otherwise normal. A chest photofluorogram was negative. The twenty-four hour urinary excretion of 17-ketosteroids was 10.2 mg. A pretreatment, twenty-four hour urinary creatine excretion was 361 mg. This and subsequent values are listed in table 2.

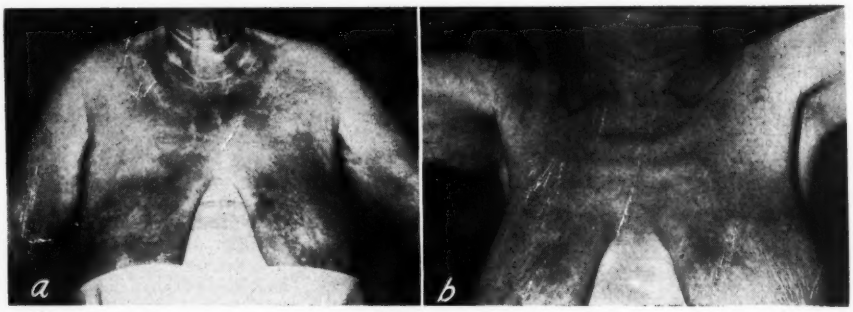

FIG. 1a. Case 1. Photograph of a patient with dermatomyositis made February 1, 1952, prior to potassium para-aminobenzoate therapy. The cutaneous eruption is evident, and there is marked weakness of the shoulder muscles: maximal abduction is depicted.

b. The same patient February 3, 1953. There is cervical adenopathy and marked weight loss associated with neoplastic disease. However, despite weight loss, there is better strength than one year previously, and improvement of the skin also is evident.

A biopsy specimen of deltoid muscle and overlying skin was taken. The sections of skin disclosed atrophy and loss of rete pegs of the epithelium, with focal aggregates of lymphocytes and plasma cells in the immediate subepithelial tissues surrounding some of the skin appendages. The muscle sections revealed some fatty infiltration, nonspecific degenerative changes, and lymphocytic cuffing of small arterioles. In addition, lymphocytes were scattered among the muscle fibers. The pathologist interpreted these findings as "probable collagen disease."

On the basis of the clinical and laboratory findings, the diagnosis of dermatomyositis was made and the patient was started on potassium para-aminobenzoate on February 7, 1952. She received 12 Gm. KPAB the first day, and 18 Gm. daily (6 doses of 3 Gm. each) thereafter. Gradual progressive improvement ensued, and by March 11, muscular strength had increased greatly while the eruption had faded considerably. The patient was discharged and continued KPAB, 18 Gm. per day, at home. A month later, she had improved further and was able to walk up and down steps. At this time, lymphadenopathy first appeared in the right anterior cervical chain. The dosage of KPAB was reduced to an average of 6 Gm. daily from May to August, 1952. There was progressive increase in muscle strength, weight gain, regrowth of hair, and fading of the eruption. Because of the persistent cervical lymphadenopathy and signs of progressive nasal obstruction, the patient was readmitted to the hospital on August 14. A cervical lymph node was removed and contained "undifferentiated malignant tumor cells which suggest an epithelial origin, possibly nasopharynx or lung." A surgical biopsy of a mass in the nasopharynx revealed an "undifferentiated carcinoma (lymphoepithelioma)."

Intensive roentgen irradiation was directed to the region of the nasopharynx, and the patient was comfortable for a few months after discharge from the hospital. The neoplasm recurred, however, and at present the patient is under roentgen-ray and nitrogen mustard therapy for extensive metastases. Clinically, the dermatomyositis is in remission. The appearance of the patient on February 3, 1953, is shown in fig. 1b. Neoplastic lymph node involvement and recent weight loss are evident, as is the improvement of the skin texture and muscle strength.

SCLERODERMA

The rationale for the use of potassium para-aminobenzoate in scleroderma is obviously similar to that which led to its use in dermatomyositis. In addition, a patient with sclerodermatomyositis exhibited such improvement in the areas of skin involvement while on para-aminobenzoic acid therapy that the treatment of further cases was indicated. In previous reports,[13, 15] detailed accounts of the results achieved in 7 patients have been given. Since then, my total experience with diffuse scleroderma has reached 40 cases, and there have been 5 other subjects with localized scleroderma, or morphea. There has been no selection of cases, every patient being treated regardless of the severity of the disease. A number had had sympathectomies, and others, extensive therapy with testosterone, cortisone, or ACTH without benefit before being placed on KPAB. Results of therapy in all 40 cases are presented in table 3.

TABLE 3.—*Duration of Therapy with Potassium Para-Aminobenzoate Related to Skin Improvement at Time of Evaluation of 40 Cases of Scleroderma.*

Skin Improvement	Period of Treatment					Total
	<1 mo.	1-3 mo.	3-6 mo.	6 mo.-1 yr.	>1 yr.	
None			1*			1
Slight	1	3†	2‡			6
Moderate		3	4§	5	5†	17
Marked		1	1	6	8	16
Total	1	7	8	11	13	40

*Softening of some areas but with appearance of new involvement during therapy.

†One patient in each group died of acute cardiac insufficiency while on treatment.

‡In one subject, weight loss continued on KPAB therapy; patient then changed to cortisone without benefit; later, succumbed to the disease.

§One patient died of a widely disseminated undifferentiated fibrosarcoma.

Characterized primarily on the basis of skin change,

1 subject who showed softening in some areas but in whom new involvement appeared during the period of therapy is listed as a failure. Slight improvement was noted in 6 patients. One of these was changed to cortisone therapy because of the disappointing result with KPAB, and he later died while receiving cortisone treatment. Two patients died of acute cardiac insufficiency and 1 of a widely metastatic undifferentiated fibrosarcoma. The latter patient was in the group of subjects who had moderate skin improvement on KPAB, of whom there were 17. Very marked improvement occurred in 16 patients. Of the subjects with morphea, all have shown moderate to marked improvement in the areas of involvement.

In addition to this experience, there are published references to satisfactory results of PABA therapy in scleroderma,[4, 9, 12] and several physicians* have kindly communicated their results in individual cases. Of these, 5 reported remarkable improvement, and another observed slower but definite progress. In another study,[3] both success and failure are reported, while two physicians* also have indicated failure in individual cases.

Experience indicates that aside from proper dosage of KPAB, duration of therapy appears to exert a major influence on the result. This is evident in table 3, which includes results in 24 patients who obtained moderate to marked improvement after receiving KPAB for from six months to more than a year. To be sure, some subjects show improvement within a few weeks. At times this may be striking. In other instances, it is only by careful checking of the involved skin over the clavicles or wrists, or about the mouth and forehead, that it is possible to note that softening of the skin has begun. Patients are usually kept on the KPAB program for many months until it is judged that no further improvement is to be expected. Some of the patients have remained on a dosage of 10 to 12 Gm. of KPAB daily for two and one-half years.

One of the major difficulties in the management of scleroderma is the problem of overcoming pericapsular and other fibrous tissue shortening. Indeed, in advanced cases the patient may have considerable improvement in skin texture without significantly improving the function of the involved part. With a few cooperative patients, the supplemental use of especially constructed dynamic traction splints has resulted in progressive stretching of the affected part. For example, fingers which at first could not be extended by the patient are gradually restored in this manner to normal position.

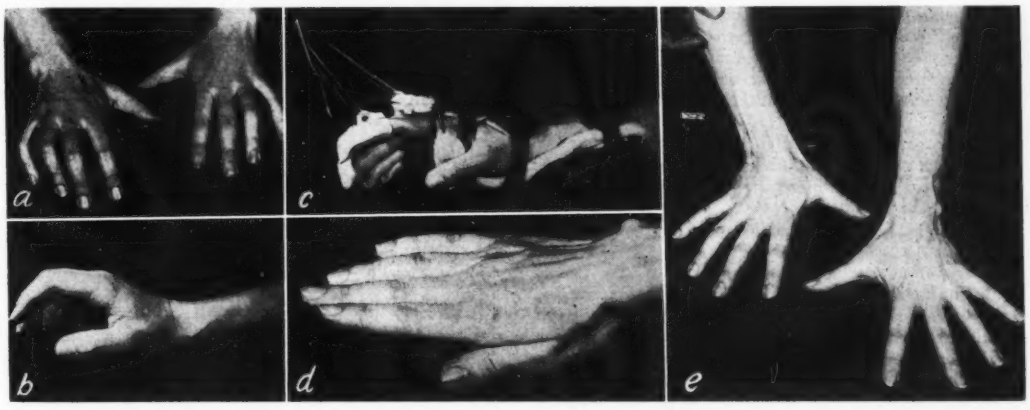

FIG. 2a. Case 2. Appearance of the hands of a patient with scleroderma on December 27, 1949, before institution of therapy.
b. Voluntary extension of the right hand of the same patient on May 26, 1950, after five months of potassium para-aminobenzoate therapy.
c. Dynamic traction splint worn on the right hand after May 26, 1950. (See text.)
d. Voluntary extension of the right hand by the patient in March, 1953.
e. Appearance of both hands in March, 1953.

Thus, in the current management of scleroderma, KPAB is administered over long periods of time, physiotherapy is instituted whenever possible, and dynamic traction splints are applied when indicated after skin softening has occurred. Aside from improvement of skin texture and in function of the involved parts, these patients frequently gain weight and have improvement in their general well-being.

The following case report illustrates many of the aforementioned factors. It is of interest also in that

A gratifying response resulted from PABA therapy in individual cases treated by the following physicians: Dr. J. R. Hendon, Louisville; Dr. R. J. Dern, Chicago; Dr. J. W. Hall, Traverse City, Mich.; Dr. J. R. Pedden, Grand Rapids, Mich.; Dr. R. J. Bolt, Ann Arbor; and Dr. I. W. Ginsburg, Philadelphia. Lack of response was reported in 1 patient treated by Dr. P. S. Steinbaum, Leonia, N. J., and in another case treated for three months by Dr. G. Bayne, Norristown, Pa.

an area of morphea was present some twenty years before the onset of generalized scleroderma. This is an unusual sequence in itself. However, the findings in this particular patient are of additional interest in that aldolase levels were determined at periods of disease activity and after improvement on KPAB therapy.

CASE 2.—E. M., a 37 year old white woman, was referred to the University Hospital at Ann Arbor on December 27, 1947, for treatment of scleroderma. She had experienced an abrupt onset of the edematous phase of scleroderma on August 6. The swelling of the hands, arms, and legs was particularly marked so that there was dimpling at the involved joints. Gradually, the edema subsided, leaving the skin firm and bound down to the subcutaneous tissues. There had been associated shortening of the underlying muscle groups of the forearms, resulting in contractures of the fingers. The calf muscles and Achilles tendons were also shortened so that she could not stand with her feet flat on the floor. An irregular low grade fever had been noted along with considerable weight loss since the onset of illness.

Examination revealed, in addition, a puffiness about the eyes. There was little pigmentary change of the skin, but there was absence of hair on the arms and legs. An oval, 5 by 10 cm. morphea-type lesion was present on the back. It had been noted by the patient for approximately twenty years.

Laboratory studies revealed the hemoglobin to be 11.5 Gm. per 100 cc., and the leukocytes numbered 5,050 per cubic millimeter with a normal differential count. Urinalysis was negative.

Baseline photographs were taken (fig. 2a) and therapy with KPAB, 12 Gm. daily, was begun December 28. Treatment was well tolerated, and four weeks later the patient had lost the edema which had been present in her face and ankles, yet had gained 6 pounds in weight. There was little perceptible change in skin texture. However, physical activity had been increased, and the patient volunteered that she could now shake down a thermometer and use a can opener.

After an additional four weeks of KPAB, the involved skin was definitely softer and there was considerable increase in range of motion of the fingers, wrists, and ankles. The muscles of the forearms also had softened somewhat. The patient was well enough to resume her occupation.

KPAB therapy was continued at the same dosage level with progressive improvement. On March 10, 1950, the aldolase activity of the patient's plasma was determined by Dr. Harold G. Petering,[30] of the Upjohn Co., Kalamazoo. The patient showed a Q_{hdp} of 60 microliters of hexose diphosphate split per hour per milliliter of plasma. This value greatly exceeds the normal range of 3 to 8 microliters for this procedure.

Progressive improvement continued, but despite softening of the skin, there was limitation of extension of the fingers, especially of the right hand. This was attributed to shortening of the pericapsular fibrous tissues. For this reason, a dynamic traction splint was constructed for the right hand, and its use added to the treatment program (fig. 2b and c). Beginning on May 27 the splint was worn for a few minutes several times daily. It was painful at first, but the patient was able to wear it for progressively longer intervals. After about a month, the splint was worn almost continually during the day. By October the fingers were essentially straight, and use of the splint was discontinued.

On June 12, 1951, another aldolase determination was made by Dr. Petering. At this time the plasma value was 9.2, slightly above the normal range.

Treatment with KPAB, 12 Gm. daily, was not stopped until July, 1951, at which time it was interrupted for two weeks, then resumed at 8 to 10 Gm. daily until April, 1952. The dosage was then gradually reduced, and KPAB was stopped on May 30.

The patient's scleroderma has since remained in remission. She was seen again March 5, 1953, at which time she appeared to be in normal health. Aside from the improvement in skin texture and joint and muscle function (fig. 2d and e), the patient had regained her normal weight. It was also of interest that only slight hyperpigmentation remained in the site of the morphea-like area.

RHEUMATOID ARTHRITIS

The results of combined treatment with potassium para-aminobenzoate and acetylsalicylic acid in 44 patients with rheumatoid arthritis recently have been described.[21] The authors were interested in confirming and extending the studies of Wiesel and others that para-aminobenzoic acid (12 Gm. daily) and cortisone in low dosage (25 mg. daily) generally suppressed the manifestations of rheumatoid arthritis without significant toxicity. Although the first patient treated by Wiesel's regimen responded well to therapy, it was discovered that this patient also was taking aspirin which had not been prescribed. Furthermore, definite relapse occurred when the aspirin was discontinued, with improvement reappearing upon its resumption. Thus, during the initial period of treatment, the patient was receiving PABA (12 Gm.), cortisone (25 mg.), and acetylsalicylic acid (2.4 Gm.). During the ensuing twenty-two months, the study of this and other subjects was conducted mainly with KPAB and aspirin, but some patients also received small doses of cortisone.

The 44 patients treated had severe rheumatoid arthritis which had progressed over the years despite courses of gold, antibiotics, transfusions, and so forth. Some had required large amounts of cortisone or ACTH, but had relapsed to their pretreatment status or worse before the KPAB–acetylsalicylic acid program was begun.

Improvement was observed in 34 of the 44 subjects treated, and was characterized by decrease in joint pain, heat, swelling, and tenderness; by increased range of motion; by diminution in size of subcutaneous nodules; by defervescence of fever when present; and often by striking gain in weight. Although the improvement after two or three weeks of therapy was occasionally remarkable, the more usual course was that of gradual betterment over several months of treatment. All of the cases listed as failures were treated for less than three months, whereas those who improved have continued treatment for from six to twenty-two months. These patients, of

course, were not cured of their rheumatoid arthritis. Some showed varying degrees of activity of the disease even though the major manifestations were suppressed. Others showed some degree of "breakthrough" of the suppressive therapy, but did not relapse to their pretreatment status during the period of observation.

DISCUSSION

The clinical course of an individual patient who has dermatomyositis, scleroderma, or rheumatoid arthritis may be unpredictable. Nevertheless, it is believed that sufficient patients with each disease have been treated with potassium para-aminobenzoate to permit a preliminary evaluation. In each group of patients, the causal relationship between therapy and response is too consistent to be attributed to chance remission. It should be emphasized, however, that KPAB is not a complete treatment for these disorders. It has failed to control cases of acute fulminating dermatomyositis and scleroderma. In highly active progressive disease, para-aminobenzoic acid may only retard the process. Nevertheless, when the disorder is moderately active, PABA therapy, as has been shown, may result in improvement which at times is striking.

Untoward reactions to KPAB have been documented previously.[13, 20, 21] Although gastrointestinal complaints are less frequent with KPAB than with other para-aminobenzoic acid preparations, anorexia and nausea still constitute the most frequent complaints. These usually subside upon omission of the drug for a day or so, and treatment may be resumed when the patient is again eating well. By omission of therapy during periods of poor dietary intake, it is also possible to prevent the occurrence of hypoglycemia as previously mentioned. The reason for the occurrence of hypoglycemia under such circumstances is poorly understood. Studies in this laboratory have ruled out renal glycosuria or a hepatic basis for this phenomenon, so that PABA appears somehow to interfere with glyconeogenesis at such times. In this connection, the study of Mayer-Gross and Walker[7] is interesting. These workers rapidly administered 20 Gm. of sodium para-aminobenzoate intravenously into each of 6 patients during insulin-induced hypoglycemic coma. No toxic effects were noted, but in 4 of the 6 subjects, there was transient restoration of consciousness.

Leukopenia has been ascribed to PABA, but it often has been present in patients prior to treatment. Nevertheless, experience with similar compounds suggests that this type of reaction is always possible, making periodic leukocyte counts advisable. In more than 400 patients treated during the course of these and other PABA investigations, however, not one case of agranulocytosis has been encountered.

Drug fever and drug rashes have occurred from the use of PABA compounds. Most of these patients may be "desensitized" by retreatment with minute quantities (for example, 1 drop of a 10 per cent solution) of the drug and by gradually increasing the dosage until full therapeutic levels are reached again.

Patients who previously have received gold, bismuth, or other heavy metal therapy may exhibit a transitory febrile response upon the administration of PABA. An interesting and presumably related phenomenon was observed in an arthritis patient who had experienced an eruption from gold therapy, followed by residual hyperpigmentation. A prompt flare-up appeared in the sites of previous skin involvement when the administration of KPAB was begun. As treatment was continued, however, the eruption gradually faded.[21]

The mechanism of action of KPAB is not known. Its beneficial effects in such widely different diseases as have been described suggests it acts at a fundamental metabolic level. It appears to suppress the nonsuppurative inflammation of lupus erythematosus and dermatomyositis, as well as of bullous disorders. In scleroderma, fibrosis not only is inhibited but appears to be reversed to a considerable degree. The altered aldolase activity observed by Petering[10] in the scleroderma patient whose case history is reported herein may be an important step in leading to a better understanding of the pathologic physiology of this disease. Other studies designed to determine the mode of action of PABA in rickettsial infections revealed that it increased cellular oxidation. It appears that PABA bypasses the cytochrome oxidase systems since the increased oxygen utilization is not blocked by potassium cyanide. In this connection, the recent investigations of Cochran are interesting.[2] Through the use of a closed-circuit Knipping type spirometer, this investigator has shown that the oral and intravenous administration of salicylates to human beings causes a marked and progressive increase in oxygen consumption. The possible relationship of these observations to the results of combined KPAB–acetylsalicylic acid therapy in rheumatoid arthritis merits study.

Additional investigations have shown that PABA has a broad absorption band for ultraviolet light, including those rays primarily responsible for sunburn erythema. PABA also appears to modify the tyrosine-dopa-melanin reactions. Other basic observations indicate that PABA participates in biosynthetic processes such as those involving the production of serine, glycine, methionine, purines, and pyrimidines.

Although the above mentioned observations are

important and emphasize the broad biologic importance of para-aminobenzoic acid, they do not offer a ready explanation of therapeutic results achieved in this and other clinical studies.

Finally, it should be evident that the present day management of scleroderma, dermatomyositis, and rheumatoid arthritis is necessarily nonspecific and will remain so until their respective etiologies have been elucidated. These disorders are all seriously debilitating; indeed, dermatomyositis and some instances of scleroderma endanger life itself. It is concluded, therefore, that properly administered, long range, high dosage KPAB therapy may be a useful adjunct in the treatment of these diseases.

SUMMARY

The clinical experiences with prolonged potassium para-aminobenzoate therapy in 9 cases of dermatomyositis, and 40 cases of scleroderma are presented. In addition, the results of therapy in 44 patients with rheumatoid arthritis who received KPAB plus aspirin are summarized.

Significant improvement was induced in a high proportion of patients treated.

The method of administration of KPAB and the necessity for long term administration of the compound are stressed.

Untoward reactions are relatively minimal and are readily reversible on stopping the drug. Hypoglycemia may be avoided by omitting therapy during periods of poor dietary intake.

It is concluded that potassium para-aminobenzoate therapy, in the doses and periods of treatment indicated, may be a useful adjunct in the management of patients with these diseases.

REFERENCES

1. Anigstein, L., and Bader, M. N.: Para-Aminobenzoic Acid—Its Effectiveness in Spotted Fever in Guinea Pigs, Science *101*:591-592 (June 8) 1945.

2. Cochran, J. B.: Respiratory Effects of Salicylate, Brit. M. J. *2*:964-967 (Nov. 1) 1952.

3. Evans, J. A.; Rubitsky, H. J.; and Perry, A. W.: Treatment of Diffuse Progressive Scleroderma, J.A.M.A. *151*:891-899 (March) 14) 1953.

4. Gougerot, H., and Hewitt, J.: Sclerodermie en Plaques, Action Combinée de L'Acide Para-Aminobenzoique et de L'A-Tocophérol, Bull. Soc. Franc. Dermat. et Syph. *58*:42-43 (Jan.-Feb.) 1951.

5. Levy, M. D., and Arnold, W. T.: Para-Aminobenzoic Acid in Treatment of Endemic Typhus Fever, Texas State J. Med. *42*:314-316 (Sept.) 1946.

6. Loewenthal, L. J. A.: Eczema and Dermatitis: Effects of Sodium Para-Aminobenzoate, South African M. J. *26*:661-664 (Aug. 16) 1952.

7. Mayer-Gross, W., and Walker, J. W.: Effect of l-Glutamic Acid and Other Amino-Acids in Hypoglycaemia, Biochem. J. *44*:92-97, 1949.

8. McGural, T. J., Jr.: Periarteritis Nodosa: Report of Case Treated with Para-Aminobenzoic Acid, Ann. Int. Med. *37*:606-611 (Sept.) 1952.

9. Norman, A.: Therapeutic Use of Sodium Salt of Para-Aminobenzoic Acid in Lupus Erythematosus, Nord. Med. *47*:318, 1952.

10. Petering, H. G.: Personal communication to the author.

11. Weiner, A. L.: Sodium Para-Aminobenzoate Therapy of Atopic Dermatitis, J. Invest. Dermat. *15*:295-296 (Oct.) 1950.

12. Wiesel, L. L.; Barritt, A. S., Jr.; and Stumpe, W. M.: Synergistic Action of p-Aminobenzoic Acid and Cortisone in Treatment of Rheumatoid Arthritis, Brooklyn Hosp. J. *8*:148-152 (July-Sept.) 1950.

13. Zarafonetis, C. J. D.: Therapeutic Possibilities of Para-Aminobenzoic Acid, Ann. Int. Med. *30*:1188-1211 (June) 1949.

14. Zarafonetis, C. J. D.; Curtis, A. C.; and Grekin, R. H.: Effects of Para-Aminobenzoic Acid in Lupus Erythematosus, Univ. Hosp. Bull. *13*:122-125 (Dec.) 1947.

15. Zarafonetis, C. J. D.; Curtis, A. C.; and Gulick, A. E.: Use of Para-Aminobenzoic Acid in Dermatomyositis and Scleroderma, Arch. Int. Med. *85*:27-43 (Jan.) 1950.

16. Zarafonetis, C. J. D.; Curtis, A. C.; and Kirkman, L. W.: Para-Aminobenzoic Acid Therapy in Lymphoblastoma Cutis and Mycosis Fungoides, Cancer, in press.

17. Zarafonetis, C. J. D.; Curtis, A. C.; and Shaw, J. M.: Treatment of Pemphigus with Potassium Para-Aminobenzoate, Abst., J. Clin. Investigation *31*:674 (June) 1952.

18. Zarafonetis, C. J. D.; Curtis, A. C.; and Shaw, J. M.; Hydroa Vacciniforme Treated with Potassium Para-Aminobenzoate, J. Invest. Dermat. *21*:5-7 (July) 1953.

19. Zarafonetis, C. J. D.; Andrews, G. A.; Meyers, M. C.; and Bethell, F. H.: Para-Aminobenzoic Acid in Leukemia, Blood, *3*:780-792 (July) 1948.

20. Zarafonetis, C. J. D.; Johnwick, E. B.; Kirkman, L. W.; and Curtis, A. C.: Para-Aminobenzoic Acid in Dermatitis Herpetiformis, Arch. Dermat. & Syph. *63*:115-132 (Jan.) 1951.

21. Zarafonetis, C. J. D.; Steiger, W. A.; Ginsburg, I. W.; and Heather, A.: Treatment of Rheumatoid Arthritis with Para-Aminobenzoate and Acetylsalicylic Acid, Arch. Int. Med. *92*:204-215 (Aug.) 1953.

ABSTRACT OF DISCUSSION

DR. BENJAMIN B. WELLS, Little Rock, Ark.: It is of interest and importance that we have our attention called to the biologic properties and therapeutic potentialities of para-aminobenzoic acid. In reporting his results, Dr. Zarafonetis has shown proper restraint while making the appropriate suggestion that this substance be given additional study and therapeutic trial.

It may be well to emphasize the fact that any beneficial effect of this or any other form of treatment in the collagen diseases is exceedingly difficult to assay. These diseases are characterized by spontaneous or nonspecifically induced remissions and are unpredictable in their course and prognosis. It must be evident that the long periods of observation followed by gradual improvements, many of which are subjective, introduce a maximal risk of spontaneous or nonspecific alteration in the disease process.

There are few, if any, studies entirely comparable to those of Dr. Zarafonetis in the use of large doses and continuous prolonged administration of PABA. Most of us have not been able to sustain our enthusiasm for the use of PABA for the time that may be required to achieve beneficial results. More persistent and intensive use of PABA may allow us to accomplish benefits such as Dr. Zarafonetis has presented.

UROLOGY AWARD

The American Urological Association again this year offers awards of $500, $300, and $200 as first, second, and third prizes respectively for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than ten years and to those in training to become urologists.

Essays must be in the office of the executive secretary, William P. Didusch, 1120 North Charles Street, Baltimore, before February 1, 1954. The first place essay will appear on the program of the American Urological Association's forthcoming meeting to be held May 31-June 3, 1954, in New York.

CLINICAL PATHOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS

BENJAMIN B. WELLS, M.D., and S. WILLIAM ROSS, M.D.,
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UNTIL quite recent times, systemic lupus erythematosus was properly regarded as a rare clinical entity not clearly distinguished from a number of equally obscure diseases and deserving little more than academic attention. Interest in the practical importance of lupus erythematosus increased progressively with the demonstration of widespread visceral lesions and the recognition of its extremely heterogeneous symptomatology. The concept of "diffuse collagen disease," introduced by Klemperer, Pollack, and Baehr in 1942,[11] suggested a histopathologic common denominator between this disease, rheumatoid arthritis, rheumatic fever, dermatomyositis, periarteritis nodosa, scleroderma, and certain other conditions. This attempt to relate a number of clinically dissimilar states through the common occurrence of demonstrable injury in the connective tissues of the body may ultimately be discarded when fundamental etiologic factors have been found. Nevertheless, the concept provided an important stimulus and approach to both clinical research and practical observation of the condition.

Among the so-called "collagen" diseases, lupus erythematosus appears to occupy a pivotal position, since it is described as having a large number of clinical and pathologic features in common with all members of the group.[17] The importance of systemic lupus erythematosus has been further emphasized by the increasing number of cases recognized during the past year or two. We were inclined at first to believe that the increased incidence could be fully ascribed to more refined methods of diagnosis and a more active interest in the disease. It now appears that these factors alone may not account for the large number of patients, many of whom present themselves with such classical and unmistakable features of systemic lupus erythematosus that a proper diagnosis would likely have been made before the advent of present methods and before the era of enthusiasm concerning the collagen diseases. In any event, systemic lupus erythematosus has acquired a position of unexpected importance both as a theoretical and practical problem for the clinician and pathologist.

From the Department of Medicine, University of Arkansas School of Medicine.

Read before the Sections on Internal Medicine and Clinical Pathology, Texas Medical Association, Annual Session, Houston, April 29, 1953.

As would be expected, a more intensive study of larger numbers of cases has forced us to revise our notions concerning the clinical course and characteristic manifestations of systemic lupus erythematosus. Because early descriptions were based on sporadic case reports or limited observations, usually made during the more severe phases of the disease, it was impossible to avoid error and disagreement. It may be fairly said that the natural history of this disease is now being rewritten, but we hasten to add that there is no suggestion of finality in our present effort.

During the past three years we have observed more than 50 cases of systemic lupus erythematosus in our clinic and associated institutions. A much larger number of patients in whom this diagnosis could not be established, but who presented certain features of lupus erythematosus or closely related diseases were studied concurrently. From the latter we obtained equally important negative and control data. For the purpose of this report we have reviewed our clinical laboratory findings in an attempt to discover those which were of most value in the practical problem of diagnosis and observation of patients under treatment. It will be evident that our experience has yielded no infallible means for either case-finding or final differentiation. As in most other studies of disease, the laboratory findings must be incorporated into the entire complex of clinical manifestations.

A complete presentation of our clinical observations will be given elsewhere. For the immediate purpose it is sufficient to tabulate the more common signs and symptoms of systemic lupus erythematosus as we have observed them in our patients (table 1).

TABLE 1.—*Common Manifestations of Systemic Lupus Erythematosus.*

Malaise, weakness, loss of body weight	Skin lesions
Arthralgia without anatomic evidence of arthritis	Pleuritis
Fever	Peritonitis
Edema and/or serous effusions	Pericarditis
Mental disturbances	Pharyngitis
Rheumatoid-like arthritis	Cutaneous photosensitivity
	Convulsions, stupor, coma

We do not believe that any one or any combination of these findings can be listed as essential to the diagnosis. Their frequency is roughly indicated by the order in which they are listed. It is necessary to keep constantly aware of the possibility of this disease, since the various manifestations tend to occur individually

or in unpredictable combinations with long intervals of quiescence or enigmatic illness. Confirmation of the diagnosis most frequently depends upon a prolonged period of observation or a meticulous history in which a convincing display of these signs and symptoms can be discovered.

From our records we have selected certain laboratory observations made on 47 patients with systemic lupus erythematosus to serve as a basis for this report. In each case a great many procedures have been carried out and in some the total period of observation has extended more than two years. It was necessary, therefore, to choose only those results which we have reason to believe typical of the disease at a particular phase or duration. For the most part we have attempted to relate the findings to three important stages: (1) the onset, or that phase in which the earliest clinical manifestations were encountered, (2) the course, at which time the more dramatic clinical features were in remission, and (3) the exacerbation, when there was evidence of renewed systemic reaction or rapid advance of the disease.

We have not concerned ourselves with the essentially benign form of lupus in which lesions are confined to the skin with little or no systemic manifestations or demonstrable visceral change. Although we have seen patients in whom the disease appeared to progress from this form into the full manifestation of systemic lupus erythematosus, we are not prepared to discuss the frequency or significance of the transition. We are not aware of any means by which the change can be predicted. Montgomery and McCreight[13] found that 22 per cent of a large series of patients with systemic lupus erythematosus had discoid lesions of the skin as an early manifestation. We are somewhat reluctant to accept the conclusion that absence of the lupus erythematosus cell phenomenon is entirely inconsistent with the diagnosis of systemic lupus erythematosus, in which event this test alone would distinguish between the benign and systemic forms of the disease. We prefer to think of systemic lupus erythematosus as a continuous disease process characterized by remissions and by chronic, subacute, and acute phases. As a whole the disease is relentless, progressive, and ultimately fatal in a high proportion of cases. In keeping with the suggestion of Arnold[1] and Haserick[8] we use the term systemic lupus erythematosus to designate the generalized form of this disease and reserve the terms "discoid" and "disseminate" to describe the skin lesions when they are present.

Criteria for any subdivisions in the course of systemic lupus erythematosus are by no means clear. Although a few cases can be recognized as acute or even fulminating and others as chronic or smouldering, many fall between the two extremes in a whole spectrum of indistinguishable shades. The striking disparity between all observations, clinical or laboratory, and the subsequent course of the disease makes it almost impossible to state an accurate prognosis. At times it is equally difficult to fix valid criteria for exacerbation following a chronic or quiescent stage.

Obviously, all of our patients have not been seen in each of the major phases upon which our data are organized; in some instances the laboratory observations are incomplete. Hence, each tabulation had to be based on a different number of results and the number is always less than the total of patients observed. Because of the essentially arbitrary and diffuse nature of these data, we do not wish to attribute statistical significance to them. Our conclusions are offered as opinions following a rather large, but essentially qualitative experience.

LABORATORY OBSERVATIONS

Erythrocyte Counts and Hemoglobin Concentration.—Anemia was found in practically all of our patients at some time during the course of systemic lupus erythematosus (table 2). Erythrocyte counts were depressed to only a mild or moderate degree in most cases. Counts less than 3,500,000 usually were associated with a protracted course of the disease or the toxic states of acute exacerbations. Even when the condition is regarded as chronic, almost one-half of the patients are reported to have a significant degree of anemia.[13] In our experience the severity of anemia has been found to parallel roughly the course of the illness and to reflect the patient's general condition fairly accurately. Hemoglobin concentrations show a similar trend, so that anemia, when present, was predominantly normochromic or only mildly hypochromic. We observed no important changes in cell volume except for slight microcytosis in association with the more severe or prolonged anemias. A generalized suppression of hematopoiesis is said to occur in systemic lupus erythematosus. Our observations of bone marrow and peripheral blood do not support this theory. The marrow generally showed normal cellularity and a normal proportion of erythrocytic precursors.

TABLE 2.—*Erythrocyte Counts in Systemic Lupus Erythematosus.*

Stage	No. Patients <2.5 M./cu. mm.	No. Patients 2.5-3.5 M./cu. mm.	No. Patients >3-5 M./cu. mm.
Onset	1	6	18
Course	6	10	14
Exacerbation	6	11	0

Peripheral leukocyte and platelet counts were usually within normal limits. The possibility of excessive red cell destruction as the cause of anemia in systemic lupus must be strongly considered. A number of cases have been reported in which acquired hemolytic ane-

mia was a salient feature.[4] Splenectomy and administration of cortisone have been found to control the hemolytic process in some cases. Splenectomy does not alter the course of the disease. Acquired hemolytic anemia with a positive Coombs test has been reported as an initial finding in some cases. In our patients we have not recognized a frank hemolytic anemia. Unfortunately, our studies do not exclude the possibility that excessive red blood cell destruction caused some of the anemia that we observed. This point needs further investigation. It has been shown that the antibody protein which is responsible for the positive Coombs test, and presumably causative of the hemolytic process, is not identical with the lupus erythematosus factor in the serum.

Leukocyte Counts.—Neutrophilic leukopenia is usually listed as typical of systemic lupus erythematosus. We were surprised to find in our patients that normal or elevated leukocyte counts were encountered more frequently than leukopenia (table 3). In 1 patient observed over a period of two years 70 total white blood cell counts were made; of these only 5 were leukopenic. White cell counts fluctuated widely during the entire course in almost all patients, responding in the usual manner to superimposed infections but generally showing no important relation to other manifestations of systemic lupus erythematosus itself. These findings are essentially confirmatory of results reported by Michael and his associates[12] in a study of 111 patients. In the latter report leukopenia was recorded as an initial finding in approximately one-third of the patients and at some time during the course of the disease in only one-half. These workers found 1 to 3 per cent of plasma cells in the peripheral blood in 15 per cent of their cases. Although we often found plasma cells increased in the bone marrow of patients with systemic lupus erythematosus, we did not recognize these cells in the peripheral blood.

TABLE 3.—*Leukocyte Counts in Systemic Lupus Erythematosus.*

Stage	No. Patients <4,000/cu. mm.	No. Patients 4,000-11,000/cu. mm.	No. Patients >11,000/cu. mm.
Onset	6	16	1
Course	5	19	13
Exacerbation	7	6	7

Platelet Counts.—Thrombocytopenia of moderate degree is usually regarded as a typical finding in systemic lupus erythematosus. Purpuric phenomena due to platelet deficiency is uncommon. Thrombocytopenia, presumably due to hypersplenism, has been reported both with and without hemolytic anemia or leukopenia.[12, 14] Hargraves[6] found an adequate number of platelets in 45 patients in whom the lupus erythematosus cell phenomenon was positive. Thrombocytopenia of significant degree was observed in only 1 case in our series. Certain observations and speculations have suggested that the blood platelets play a fundamental role in the pathogenesis of systemic lupus erythematosus.[6] It appears, however, that thrombocytopenia of clinical significance is decidedly uncommon. We also found no abnormal clotting or bleeding times among our patients.

Sedimentation Rate.—We have nothing new to add on the sedimentation rate. As in many other chronic conditions, the sedimentation rate appeared to parallel rather accurately the course of systemic lupus erythematosus. Using the technique of Wintrobe, we found increased rates in our patients when any other evidences of active disease could be found, and not infrequently it was our only important evidence of continuing disease. Sedimentation rates greater than 20 mm. per hour were recorded in about 95 per cent of all observations made in this series.

Examination of Bone Marrow.—Analyzing the bone marrow examinations of 26 patients with systemic lupus erythematosus, we found 17 entirely within normal limits. In 5 cases the only unusual feature was a moderate increase in plasma cells; in 4 the count was 5 per cent or less, and in 1 marrow we counted 10 per cent of plasma cells. We are unable to attach any particular significance to this finding. We have found more marked increases in plasma cells of the bone marrow in patients with active rheumatoid arthritis.[19] In 1 bone marrow we observed a moderate myeloid hyperplasia, probably related to intercurrent infection. In 2 there was a moderate erythroid hyperplasia which we thought was adequately explained by recent blood loss. In only 1 instance did we feel justified in describing the bone marrow as mildly hypoplastic or, at least, hypocellular.

Plasma Proteins.—An increase in plasma globulin with reversal of the albumin-globulin ratio is said to characterize the acute phases of systemic lupus. We found globulin levels above 4 Gm. per 100 cc. in only about 20 per cent of our patients. Hyperglobulinemia occurred in only 2 of 14 patients observed at the onset of the disease, and was noted in approximately one-half of the patients considered to be in exacerbation. We found 3 instances in which hyperglobulinemia was striking, 1 having a total protein concentration of 12 Gm. per 100 cc. with 8.5 Gm. of globulin.

Much theoretical importance is ascribed to plasma protein changes in systemic lupus erythematosus,[3, 5] although most of the changes are not detected by ordinary clinical laboratory methods. In view of the fact that hyperglobulinemia occurs in a number of other conditions, some of which have clinical features in common with lupus erythematosus, the diagnostic significance of this observation is further reduced. Increases in the gamma-globulin and alpha-2-globulin

fractions as demonstrated electrophoretically by Reiner[16] and by Walker and Benditt[18] are undoubtedly more specific. Ehrich[5] has formulated an interesting theory for the pathogenesis of all the collagen diseases in which an abnormal gamma globulin, presumably produced by plasma cells, is assumed as the common denominator. The abnormal globulin is supposed to be carried in the blood, and in some way it produces injury to the mesenchymal tissues. Ehrich proposed the term "dysgammaglobulinemia" to designate the entire group of diseases thought to have this pathogenic mechanism. An appreciable amount of cryoglobulin has been reported in the plasma of some patients with systemic lupus erythematosus.[2] This abnormal protein, which is characterized by its precipitation from the plasma at temperatures below 37.5 C., has been found in association with Raynaud's phenomenon and in nonthrombocytopenic purpura. Its full significance has not been determined. We found cryoglobulin in the plasma of only 1 of our patients, but its presence was excluded in only a small proportion of our cases. We were not able to induce the L. E. phenomenon in vitro by addition of cryoglobulin separated from this patient's serum.

Urinalysis and Renal Failure.—Abnormal urinary findings were always observed at some time during the course of the disease. Albuminuria was present in more than 90 per cent of the urines examined and was accompanied by microscopic hematuria, pyuria, and cylinduria in approximately 60 to 70 per cent. Gross hematuria occurred in 3 patients. We were unable to note any specific relation between abnormal constituents of the urine and the stage or severity of the disease. The abnormalities tended to be more marked at the same time that other evidences of active disease were present and in the patients who developed renal insufficiency. It may be said that when there is clinical evidence of active disease, a completely normal urinalysis is so uncommon as to cast serious doubt on the diagnosis of systemic lupus erythematosus.

Signs of renal failure have appeared thus far in more than one-third of our patients. This figure is based on the finding of blood nonprotein nitrogen in excess of 40 mg. per 100 cc., not explained by extrarenal factors, and/or a low fixed specific gravity of the urine. Although as noted above, abnormal constituents of the urine are found rather early and almost continuously during the course of systemic lupus erythematosus, actual renal failure is usually a late or even a terminal event. It would appear from some reports that postmortem findings show a more marked and more frequent involvement of the kidneys than is reflected by laboratory evidence during life.[9, 15] We object to this conclusion, since urinary findings appear almost universally in patients with systemic lupus erythematosus and signs of renal failure are common, while histopathologic changes in the kidney are not infrequently minimal or lacking. Evidence of advanced or progressive renal damage is without doubt the most serious prognostic sign to be observed in the course of systemic lupus. A few of our patients, however, are surviving with normal blood chemistry after uremic episodes in which nonprotein nitrogen levels were in excess of 100 mg. per 100 cc.

Liver Function Tests.—In the series of cases reviewed by Reifenstein and associates[15] perihepatitis and hepatomegaly associated with peritonitis were found frequently. Jaundice has been described as an occasional occurrence and abnormal liver function tests have been noted.[10] No cases have come to our attention in which hepatitis was a serious problem. Thymol turbidity tests and cephalin cholesterol flocculation tests were positive in almost 20 per cent of our patients. Since these results may have been due to plasma protein changes, they cannot be taken as a definite indication of hepatocellular damage. A subclinical degree of icterus was noted in 3 patients and bromsulphalein retention was found in 3. Needle biopsy of the liver was carried out in only 5 cases. In 4 of these there were changes consistent with the diagnosis of hepatitis.

Cerebrospinal Fluid.—Lesions of the central nervous system are more common in systemic lupus erythematosus than is generally appreciated. We encountered a number of striking instances in our series of observations. Previous reports have noted increases in the spinal fluid protein, usually without pleocytosis, associated with these lesions. We had occasion to examine the cerebrospinal fluid in 10 of our patients. In 3 of these there was a definite increase in cells (lymphocytes) and in 4 the protein content was between 60 and 100 mg. per 100 cc. In all instances the complement fixation test for syphilis was negative.

Biopsy Procedures.—We do not believe that discussion of histopathologic findings is within the scope of this report. It may be mentioned, however, that we took biopsy samples of skin lesions from 13 of the patients in this series. In 11 the lesions were reported as consistent with the diagnosis of lupus erythematosus; in 2 the tissue findings were indeterminate. We doubt the specificity of histopathologic changes in the skin in this disease and believe that the gross appearances are as reliable in most instances. Histologic examination is indicated, of course, when the gross description is highly atypical or when unrelated diseases must be ruled out.

Subcutaneous nodules were removed for examination in 3 cases. These were found to be histologically indistinguishable from the periarticular nodules of rheumatic fever or rheumatoid arthritis. Enlarged

lymph nodes from 4 patients were described as showing only nonspecific adenitis. Of 3 muscle specimens only one showed a so-called nodular polymyositis. We do not regard this finding as specific and made no effort to secure additional muscle biopsies during the later progress of this study.

Miscellaneous Laboratory Results.—False positive serologic tests for syphilis have frequently been noted in systemic lupus erythematosus. In one series, false positive reactions were reported in 43 per cent of the cases. Using the standard Kahn procedure, we found 4 false positive reactions in 30 patients. On the first repeat examination, 2 of these were negative. This inconstancy of the false positive reaction is characteristic, and repetition of the test will resolve the problem in most cases.

All bacteriologic examinations were noncontributory. Forty-six blood cultures were negative. Pleural and peritoneal fluids were examined, each in 3 patients. The only interesting property of these fluids was a relatively large content of protein, between 4 and 5 Gm. per liter in 4 instances, without a comparable number of inflammatory cells.

We carried out the sheep cell agglutination test for rheumatoid arthritis in 14 patients of this series.[10] In 5 there was agglutination at a dilution of 1:56 or greater. The significance of this result is unknown.

L. E. Cell Phenomenon.—Since the original description by Hargraves, Richmond, and Morton many modifications of the L. E. cell test have been recorded.[17] All of the procedures can be put into two general categories: (1) demonstrations of the L. E. cell in the patient's bone marrow or peripheral blood and (2) in vitro production of the L. E. cell phenomenon. In the first group, leukocytes are obtained by taking the buffy layer from the patient's blood or bone marrow; after an appropriate period of incubation, smears are made and stained by Wright's technique. In the second group of tests, the patient's serum or plasma is incubated with a concentrated leukocyte preparation obtained from normal human or animal blood or bone marrow; smears are prepared and studied in the same manner. Modifications in both forms of the procedure generally have to do with various means of obtaining the buffy layer or concentrated leukocyte preparations: for example, the use of various anticoagulants, defibrination methods, teasing out the clot.

Except for supravital staining techniques, we have introduced all of the published methods into this study. A total of more than 400 patients have been examined using multiple and repeated test procedures. More than 60 different diseases have been included in the study: all of the so-called collagen diseases, discoid lupus, multiple myeloma, various leukemias, pernicious anemia, and a number of conditions characterized by hyperglobulinemia. We have encountered no false positive result in this series. In several instances a positive L. E. cell test has been obtained before the characteristic clinical manifestations were observed. In all of these cases the positive test was fully confirmed by the subsequent development of unmistakable signs and symptoms or by autopsy findings. Our results in this connection are in accord with the reports of more than 3,000 such tests that we found in the medical literature.[17] Although some false positive L. E. tests have been reported, their number is so small that the subject appears to deserve no serious consideration. Perhaps the most common cause of an apparent false positive result is the presence of amyloid in the bone marrow, usually associated with multiple myeloma. One must be aware of this possibility; it can usually be detected by differential staining of the amyloid particles. The possibility of various fungi producing L. E.–like cells appears to be eliminated by the simple expedient of clean glassware and fresh solutions.[7]

We found that each of the various methods gave about the same proportion of reliable results. It is important to note, however, that one method may be positive when another is negative without any apparent reason or constancy. For this reason, we think that at least two testing procedures should be used before a negative result is reported.

In general, the more acute cases yielded a larger percentage of positive tests and the more chronic cases often showed negative tests (table 4). Among our chronic cases of systemic lupus erythematosus we had a significant number of false negative results. We also found negative results during spontaneous or cortisone induced remissions in patients who previously had positive tests. We also know that false negative results can be produced by certain technical digressions of which the following are most common: (1) excessive dilution of the reaction mixture, (2) inhibition of phagocytosis by anticoagulants or physical mishandling of the material, and (3) bacterial contamination.

TABLE 4.—*Tests for L. E. Phenomenon.*

Clinical Phase	Bone Marrow		Peripheral Blood		In Vitro Tests	
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
Acute	11	1	7	2	5	1
Subacute	9	4	11	2	4	4
Chronic	0	5	0	4	0	3

SUMMARY

Clinical laboratory findings on 47 patients with systemic lupus erythematosus are reported and discussed. The expected leukopenia and hyperglobulinemia were not observed in a large proportion of these cases. Anemia, increased sedimentation rate, and abnormal urinalysis were among the most consistent

findings recorded. No test presently available has specific diagnostic value except the demonstration of L. E. cells in bone marrow or peripheral blood or the L. E. factor in the patient's serum. The L. E. phenomenon may be absent during chronic phases of systemic lupus erythematosus and during spontaneous or induced remissions of the disease.

REFERENCES

1. Arnold, H. L., Jr.: Systemic Lupus Erythematosus, Arch. Dermat. & Syph. *62*:632-634 (Nov.) 1950.
2. Barr, D. P.; Reader, G. C.; and Wheeler, C. H.: Cryoglobulinemia. Report of Two Cases with Discussion of Clinical Manifestations, Incidence and Significance, Ann. Int. Med. *32*:6-29 (Jan.) 1950.
3. Coburn, A. F., and Moore, D. H.: Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. *73*:196-221 (Sept.) 1943.
4. Dubois, E. L.: Acquired Hemolytic Anemia as Presenting Syndrome of Lupus Erythematosus Disseminatus, Am. J. Med. *12*:197-204 (Feb.) 1952.
5. Ehrich, W. E.: Nature of Collagen Diseases, Am. Heart J. *43*:121-156 (Jan.) 1952.
6. Hargraves, M. M.: L. E. Cell Phenomenon, Proc. Staff Meet., Mayo Clin. *27*:419-423 (Oct. 22) 1952.
7. Haserick, J. R.: Simulation of Lupus Erythematosus Phenomenon by Materials of Fungal Origin, J. Invest. Dermat. *16*:211-215 (April) 1951.
8. Haserick, J. R.: Plasma L. E. Test in Systemic Lupus Erythematosus, J.A.M.A. *146*:16-20 (May 5) 1951.
9. Keith, N. M.: Renal Problem in Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. *15*:682-683 (Oct. 23) 1940.
10. Klemperer, P.; Pollack, A. D.; and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. *32*:569-631 (Oct.) 1941.
11. Klemperer, P.; Pollack, A. D.; and Baehr, G.: Diffuse Collagen Disease: Acute Disseminated Lupus Erythematosus and Diffuse Scleroderma, J.A.M.A. *119*:331-332 (May 23) 1942.
12. Michael, S. R.; Vural, I. L.; Bassen, F. A.; and Schaefer, L.: Hematologic Aspects of Disseminated (Systemic) Lupus Erythematosus, Blood *6*:1059-1072 (Nov.) 1951.
13. Montgomery, H., and McCreight, W. G.: Disseminated Lupus Erythematosus, Arch. Dermat. & Syph. *60*:356-372 (Sept.) 1949.
14. Pisciotta, A. V.; Giliberti, J. J.; Tibor, J. G.; and Engstrom, W. W.: Acute Hemolytic Anemia in Disseminated Lupus Erythematosus, Am. J. Clin. Path. *21*:1139-1144 (Dec.) 1951.
15. Reifenstein, E. C.; Reifenstein, E. C., Jr.; and Reifenstein, G. H.: Variable Symptom Complex of Undetermined Etiology with Fatal Termination, Arch. Int. Med. *63*:553-574 (March) 1939.
16. Reiner, M.: Effect of Cortisone and Adrenocorticotropin Therapy on Serum Proteins in Disseminated Lupus Erythematosus, Proc. Soc. Exper. Biol. & Med. *74*:529-531 (July) 1950.
17. Ross, S. W., and Wells, B. B.: Systemic Lupus Erythematosus: Review of Literature, Am. J. Clin. Path. *23*:139-160 (Feb.) 1953.
18. Walker, S. A., and Benditt, E. P.: Serum Proteins in Diseases of Connective Tissue; Electrophoretic Study, J. Invest. Dermat. *14*:113-120 (Feb.) 1950.
19. Wells, B. B.; Ross, S. W.; and Lowrey, R. D.: Laboratory Aids in Diagnosis and Treatment of Rheumatoid Arthritis, Texas State J. Med. *47*:700-705 (Oct.) 1951.

ABSTRACT OF DISCUSSION

DR. C. T. ASHWORTH, Fort Worth: The data presented here by Dr. Wells and Dr. Ross have been especially useful in demonstrating the variability of the clinical picture of systemic lupus erythematosus, and particularly in showing some of the abnormalities that may be expected in the laboratory procedures used in the study and diagnosis of this entity.

It is certainly a surprise to know that leukopenia has not been a more constant finding, inasmuch as this usually has been counted as one of the more important laboratory signs. It is well that some consideration has been given to the possibility that the anemia, leukopenia, and thrombocytopenia, if present, may be due to hypersplenism, but I am glad to see conservatism in the interpretation of splenic participation, since I believe there is a real trend to over-diagnose this phenomenon at the present time as a cause of anemia.

The experiences reported here and elsewhere by Dr. Wells and his group on the demonstration of L. E. cells have been an important contribution. It is a relief to me to know that a good many of the cases of more protracted lupus will fail to give the L. E. phenomenon and that it is the more acute cases which can be counted on to be positive in this respect. I mention this because we have been discouraged by negative results in this test in several cases which clinically appeared to be chronic lupus.

The evidence cited on plasma cell increases in the bone marrow in lupus is of great interest, and it begins to appear at last that plasma cells are to have some type of demonstrated function. I am wondering if the essayists would go so far as to suggest that the L. E. protein might be a product of plasma cells, and if it is thought there might be some relationship chemically, or otherwise, to the Bence-Jones protein of plasma cell myeloma. The fact that L. E. cells also can be demonstrated in some cases of multiple myeloma serves further to emphasize that there may be some related disturbance in the plasma proteins in the two diseases.

Another condition which may have to be considered as a cause of the false positive L. E. test is penicillin hypersensitivity reactions, since 3 such cases have been reported recently.

I am much interested to learn that in 3 cases subcutaneous nodules which resembled rheumatoid nodules were removed. This serves to indicate further a relationship between rheumatoid arthritis and lupus erythematosus. Also, it may suggest an answer to those cases in which subcutaneous, juxta-articular nodules of the same specific histologic structure are found in patients, usually men, who have no clinical evidence of either lupus or rheumatoid arthritis. The question might be posed, are these cases of a mild type of systemic lupus erythematosus?

DR. WELLS, closing: It is true that leukopenia generally accompanies the acute and more active phases of systemic lupus erythematosus. The diagnosis can be made, and most often will be made, however, when the disease is relatively quiescent. In the latter circumstance, our results indicate that leukopenia is not a reliable diagnostic feature.

The production of an abnormal protein by plasma cells may well be important in the pathogenesis of the collagen diseases and may relate these to certain more remote conditions associated with hyperglobulinemia. At present there is insufficient evidence to justify elaboration of a theory upon this interesting suggestion.

ARTHRITIS RESEARCH FELLOWSHIPS

The Arthritis and Rheumatism Foundation is offering three research fellowships for basic research in arthritis. They are predoctoral fellowships ranging from $1,500 to $3,000 per annum tenable for one year with prospect of renewal; postdoctoral fellowships ranging from $3,000 to $6,000 per annum with prospect of renewal; and senior fellowships for experienced investigation with an award of $6,000 to $7,500 per annum tenable for five years. Deadline for applications is November 1, and awards will be made by February 15.

Further information and application forms may be obtained from the medical director of the foundation, 23 West Forty-Fifth Street, New York 36.

Clinical Effects of Khelltron in Angina Pectoris

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KHELLIN is the active principle of Ammi visnaga, an Egyptian plant which has been used for many decades for the treatment of ureteral colic. Prepared by Mustapha[15] in 1879 and studied biologically by Samaan[17] in 1932, it was introduced as a coronary vasodilator in 1945 by Kenawy and Barsoum.[12] The Egyptians[1, 2] under Anrep demonstrated that khellin causes a conspicuous dilatation of the coronary arteries in the heart-lung preparation, which, although less than that of amyl nitrite, is more prolonged. On comparative tests with aminophylline, it was found at least four times as powerful as a coronary vasodilator.

Numerous reports have appeared in the literature regarding the clinical effectiveness of khellin. Anrep and his co-workers[1] found that khellin given orally to 250 patients with mild to severe angina produced distinct improvement in 140 and moderate improvement in an additional 85. Most investigators[3, 5, 6, 8] have reported favorable results, but a few[10, 11] found it of little value.

Toxic symptoms, principally anorexia, nausea, vomiting, and dizziness, have been a major hindrance to persistent use of the drug. Although Anrep and others[1] noted them in only a few cases, such side effects have occurred in more than 60 per cent of most series.

Enteric coated preparations have shown little success in diminishing side effects. Purified crystalline khellin gave some promise of better tolerance,[18] but this has not been borne out in a more recent study.[7] Although parenteral khellin has been observed to be of value,[13] in our experience it has caused severe pain at the site of injection, and also has often produced nausea and vomiting. Apparently the toxic symptoms are at least in part of central origin.

The use of antispasmodics with khellin is an attempt to achieve therapeutic effectiveness without symptoms of intolerance. Khelltron is a preparation containing 20 mg. of crystalline khellin, 40 mg. of Sestron Monocitrate, and 3 mg. of thiamine hydrochloride. It was hoped that this combination not only would decrease the incidence of toxic effects, but also would increase the vasodilatory action.

Sestron, also known as Profenil, is a tertiary amine of the aliphatic-aromatic series. Studies[9] of toxicity in rats revealed no toxic symptoms after heavy dosage for from thirty-six to sixty days, and no cumulative toxicity could be detected. Animal assays of acute toxicity showed theoretical margins for single doses to be 1:60 for parenteral application and at least 1:170 for oral administration. It is a smooth muscle depressant and, in common with other smooth muscle depressants such as papaverine, nitrites, and histamine, lowers blood pressure. It is active in conditions in which it is desired to reduce smooth muscle spasm, such as spastic conditions of the gastrointestinal tract, hyperemesis gravidarum and seasickness, and circulatory spasms. Clinical reports[14, 20] of the use of Sestron as an antispasmodic have been favorable.

We have used Khelltron in the therapy of angina pectoris in a controlled study at the University of Texas School of Medicine for the past fifteen months.

MATERIAL AND METHODS

Only ambulatory patients with clear-cut angina pectoris relieved by nitroglycerine were selected for the study. The anginal symptoms in all cases had been of at least six months' duration, during which time there had been no evidence of myocardial infarction or of marked change in symptoms. An analysis of the clinical material is presented in table 1. Most of the patients were in the sixth and seventh decades of life, and there was a preponderance of males. Eighteen of the patients definitely had sustained a previous, recorded episode of myocardial infarction.

TABLE 1.—*Data on 41 Patients Treated with Khelltron.*

Age	No. Patients	Sex	No. Patients
30-39	2	Male	26
40-49	4	Female	15
50-59	12	Race	No. Patients
60-69	13	White	21
70-79	7	Negro	20
80-89	3		

Type of Heart Disease	
Arteriosclerotic and hypertensive	23
Arteriosclerotic	13
Syphilitic and arteriosclerotic	3
Previous myocardial infarction	18

Preliminary electrocardiograms were done in all cases. Only one tracing was within normal limits, and the exercise tolerance test in this patient was positive. There were electrocardiographic evidences of old myocardial infarction in 8, left ventricular hypertrophy in 15, left bundle branch block in 2, and right bundle

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Supported in part by the H. H. Weinert Fund for Cardiovascular Research. The Khelltron used in this study was furnished by the U. S. Vitamin Corporation.

Read before the Section on Internal Medicine, Texas Medical Association, Annual Session, Houston, April 29, 1953.

branch block in 1. Four patients were being treated with maintenance doses of digitalis, but none had congestive heart failure.

During a control period of at least two weeks, the patient was instructed to record each anginal episode requiring nitroglycerine in order to establish a baseline. Then administration of Khelltron was begun, generally in doses of 1 tablet (containing 20 mg. of crystalline khellin, 40 mg. of Sestron Monocitrate, and 3 mg. of thiamine hydrochloride) three times daily with or after meals. A detailed written record of the frequency of anginal episodes and of any side effects was maintained. At the end of two weeks, if there had not been more than 50 per cent decrease in the incidence of angina, the dose was increased to 2 tablets three times daily. This dosage was continued for two weeks more, and in 2 patients further increased to 3 tablets three times daily. Then, unknown to the patient, placebos identical in appearance to the active product were substituted for two weeks, and the record of anginal episodes was continued. In many of the patients, the effective Khelltron dosage was then alternated with the placebos in two-week periods.

In some of the patients, khellin had been administered prior to the study, and results were available for comparison. In others, Peritrate was subsequently administered. In 10 patients, Khelltron has been given for more than six months without any changes in the blood count or any toxic manifestations.

TABLE 2.—*Response to Khelltron in Angina Pectoris.*

Severity of Disease (No. Patients)	3 Tablets/Day Improvement			6 Tablets/Day Improvement			9 Tablets/Day Improvement		
	No	Mod.	Mkd.	No	Mod.	Mkd.	No	Mod.	Mkd.
Mild (11)	4	2	1	0	1	6			
Moderate (20)	4	4	6	2	5	2			2
Severe (10)	3	2	3	0	5	4			
Total (41)	11	8	10	2	11	12			2

TABLE 3.—*Analysis of Response to Khelltron and to Placebos in Angina Pectoris and Toxic Effects of Khelltron.*

Severity of Disease (No. Patients)	No Improvement or Placebos 50% as Much	Definite Improvement	Toxicity and Withdrawal	Improvement Without Toxicity
Mild (11)	5	6, Mkd. in 4	1	5
Moderate (20)	6	14, Mkd. in 7	5	9
Severe (10)	3	7, Mkd. in 5	2	5
Total (41)	14	27, Mkd. in 16	8	19

RESULTS

The angina was arbitrarily classified as "mild" if episodes during the control period occurred less than 7 times per week, "moderate" if from 7 to 30 per week, and "severe" if more than 30 per week. Table 2 presents the clinical results upon administration of Khelltron, before consideration of placebo or toxic effects. There was considered to be no improvement if the incidence of attacks were reduced less than 50 per cent from the control period, moderate improvement if reduced from 50 to 90 per cent from the control period, and marked improvement if reduced more than 90 per cent or if angina completely disappeared. Of the 29 patients given 3 tablets per day, 8 showed moderate and 10 marked improvement. Of 25 patients given 6 tablets per day, 11 showed moderate and 12 marked improvement. Both patients who were given 9 tablets per day showed marked improvement.

Table 3 presents the data with improvement analyzed in relation to the placebo administration and toxic effects. If Khelltron produced less than 50 per cent reduction in incidence of angina from the control period, or if the placebo therapy resulted in more than half as much improvement as did the Khelltron, the patient was considered a treatment failure. According to these criteria, Khelltron failed to elicit definite improvement in 14 of the total of 41 patients. The remainder, or 27, were judged to show definite improvement to Khelltron therapy. However, of this group 8 had to discontinue the medication because of toxic effects. The remaining 19 patients achieved definite improvement on Khelltron without toxicity. The percentage of treatment success was approximately constant in the three grades of angina pectoris.

The toxic effects of Khelltron are presented in table 4. Toxic symptoms, which were evident in roughly one-fourth of the patients, usually appeared during the first several days of administration, but in a few cases were not noted until the second week.

TABLE 4.—*Khelltron Toxicity.*

Khelltron (Tablets/Day)	No. Patients	Toxicity
3	29	8; discontinued in 6 (nausea 2, nausea & vomiting 4, nausea & diarrhea 1, dizziness 1)
6	25	7: discontinued in 5 (nausea 1, nausea & vomiting 6)
9	2	0

Fourteen of the patients previously had been given khellin. Eight of these who had been given 120 mg. of khellin per day had had toxic symptoms. When transferred to equivalent doses of Khelltron, none of

the patients who tolerated khellin well had any side effects. Of the 8 patients who became toxic on khellin, 1 became more toxic, 2 had equal toxicity, 2 had less toxicity, and 3 had no symptoms of toxocity when given Khelltron.

Table 5 presents a comparison of the therapeutic and toxic effects in 11 patients who were subsequently given Peritrate in doses of 10 mg. four times daily, after having received Khelltron, 6 tablets per day. Four were judged to have better results with Khelltron, 3 had similar effects with both, and 5 had better results with Peritrate.

DISCUSSION

The evaluation of response to specific therapy in angina pectoris is difficult. The natural history of the disease is one of considerable variation, and many factors operate to change the incidence of the attacks. For this reason, we attempted to select patients whose condition had been static for a number of months prior to the study and who had not had a recent myocardial infarction.

No study of this type can be adequate unless at times placebos of the exact appearance of the active drug are administered unknown to the patient. Our method was first to administer Khelltron, and then, when an adequate response had been achieved, to substitute the placebo. The effects of khellin are cumulative and tend to persist. Thus during the first few days of placebo therapy khellin effects were probably still present. Thus we thought that our results would tend to be balanced in favor of the placebos.

The incidence of definite improvement in this series (about two-thirds) is approximately similar to that noted in many clinical reports—60 per cent by Armbrust and Levine,[3] 71 per cent by Conn and others,[6] 140 of 250 by Anrep and others,[1] 19 of 23 by Ayad.[4] However, 8 patients of the 27 with improvement had toxic effects requiring withdrawal. Anrep and his associates[1] had no significant toxic effects in their large series. Likewise, Dewar and Grimson[8] in 12 patients noted no unpleasant side effects in therapeutic doses. However, Armbrust and Levine[3] noted uncomfortable side effects in 60 per cent of their patients; Rosenman and others[16] reported 39.5 per cent reactions; Scott and others[19] 85 per cent; Conn and others[6, 7] 62 per cent with khellin and 50 per cent with the more purified crystalline khellin.

It is our impression that effectiveness of Khelltron is approximately similar to that of other khellin preparations. However, from comparison with the results in the literature, and from our own personal experiences, the unpleasant side effects of Khelltron are only about one-half as frequent. Thus from the standpoint of reduced toxicity, it appears to be preferable to the ordinary khellin preparations in the therapy of angina pectoris. Dosage should be begun at a low level (3 tablets per day) and increased according to the response of the patient.

TABLE 5.—*Summary of Results in 11 Patients Given Khelltron and Peritrate.*

Better Results with Khelltron (No.)	Same (No.)	Better Results with Peritrate (No.)
2—Mkd. improvement with Khelltron; none with Peritrate	2—Mkd. improvement with both	2—Mkd. improvement with Peritrate; less than 50% with Khelltron.
2—Khelltron stopped pain; 50% less with Peritrate	1—Neither effective; both resulted in nausea and vomiting	1—Mod. improvement with both, but nausea on Khelltron.
		2—Mod. improvement with Peritrate; no definite improvement with Khelltron, and nausea and vomiting.

SUMMARY AND CONCLUSIONS

Khelltron, a combination of crystalline khellin 20 mg., Sestron Monocitrate 40 mg., and thiamine hydrochloride 3 mg. was administered to 41 ambulatory patients with angina pectoris. The therapeutic effects were analyzed and compared to symptoms during a preliminary control period, placebo therapy, and in some instances treatment with khellin and Peritrate.

Khelltron produced definite improvement in 27 of the patients. However, it had to be discontinued in 8 of these because of toxic effects. Thus 19 experienced definite improvement without toxicity.

Incidence of side effects appeared about one-half as frequent as with khellin, being noted in less than one-third of the entire series.

The therapeutic effectiveness of Khelltron is similar to that of khellin, but less frequent toxic effects would make it preferable. It should be tried particularly in patients who obtain relief with other khellin medication but develop unpleasant side effects.

REFERENCES

1. Anrep, G. V.; Kenawy, M. R.; and Barsoum, G. S.: Coronary Vasodilator Action of Khellin, Am. Heart J. 37:531-542 (April) 1949.

2. Anrep, G. V.; Barsoum, G. S.; Kenawy, M. R.; and Misrahy, G.: Ammi Visnaga in Treatment of Anginal Syndrome, Brit. Heart. J. 8:171-177 (Oct.) 1946.

3. Armbrust, C. A., Jr., and Levine, S. A.: Treatment of Angina Pectoris with Preparation of Khellin (Ammi Visnaga), Am. J. M. Sc. 220:127-132 (Aug.) 1950.

4. Ayad, H.: Khellin in Angina Pectoris, Lancet 1:305 (Feb. 21) 1948.

5. Best, M. M., and Coe, W. S.: Effect of Khellin on Coronary

Artery Insufficiency as Evaluated by Electrocardiographic Tests, Circulation *2*:344-350 (Sept.) 1950.

6. Conn, J. J.; Kissane, R. W.; Koons, R. A.; and Clark, T. E.: Treatment of Angina Pectoris with Khellin, Part I, Ann. Int. Med. *36*:1173-1178 (May) 1952.

7. Ibid., Part II, Ann. Int. Med. *38*:23-27 (Jan.) 1953.

8. Dewar, H. A., and Grimson, T. A.: Khellin in Treatment of Angina of Effort, Brit. Heart J. *12*:54-60 (Jan.) 1950.

9. Freedman, L.: Personal communications to the author.

10. Greiner, T., and Gold, H.: Method for Evaluation of Effect of Drugs on Cardiac Pain of Angina of Effort: Study of Khellin, Abst., J. Pharmacol. & Exper. Therap. *98*:10 (Jan.) 1950.

11. Hultgren, H. N.; Robertson, H. S.; and Stevens, L. E.: Clinical and Experimental Study of Use of Khellin in Treatment of Angina Pectoris, J.A.M.A. *148*:465-469 (Feb. 9) 1952.

12. Kenawy, M. R., and Barsoum, G. S.: Ammi Visnaga in Treatment of Anginal Syndrome, Gaz. Faculty Med. Cairo *13*:39, 1945.

13. Kleiber, E. E.: Parenteral Administration of Amnivin (Khellin) in Treatment of Coronary Disease, Ann. Int. Med. *36*:1179-1189 (May) 1952.

14. Mantell, C., and Kovnat, M.: Spasmolysis Problems in General Practice, M. Times, New York *74*:305-307 (Nov.) 1946.

15. Mustapha, I.: Ammi Visnaga, Compt. rend. Acad. d. sc. *89*:442, 1879.

16. Rosenman, R. H., and others: Observations on Clinical Use of Visammin (Khellin), J.A.M.A. *143*:160-165 (May 13) 1950.

17. Samaan, K.: Pharmacological Action of Visammin, Quart. J. Pharm. & Pharmacol. *5*:6-20 (Jan.-March) 1932.

18. Scott, R. C., and Seiwert, V. J.: Treatment of Angina Pectoris with Pure Crystalline Khellin, Ann. Int. Med. *36*:1190-1197 (May) 1952.

19. Scott, R. C., and others: Studies on Effect of Oral and Parenteral Administration of Visammin (Khellin) in Patients with Angina Pectoris, Circulation *3*:80-88 (Jan.) 1951.

20. Weiss, S.: Profenil—New Antispasmodic; Preliminary Report, Rev. Gastroenterol. *12*:436-439 (Nov.-Dec.) 1945.

ABSTRACT OF DISCUSSION

DR. EDGAR MCPEAK, Houston: Whatever the sequence of physiologic effects initiated by nitroglycerine to restore a balance in coronary blood flow and to relieve the anginal episode, physicians would like to find some therapeutic agent to maintain this balance and either control or prevent the onset of attacks.

In spite of the prolonged and arduous search for drugs of this nature, nitroglycerine and therapeutic discipline remain fundamental in rendering life tolerable for the average anginal patient. Forms and combinations of the longer acting nitrite, papaverine, and khellin groups of drugs have come under the most recent investigative attention. It is interesting to note that under the particular confines of the studies presented there appears to be little choice between any of these drugs, except as may relate to their individual toxic effects.

The disagreeable side effects of khellin occurred so frequently, as compared to any favorable influence attributable to its use, in my early experience with the drug that it was soon abandoned. It appears from this study that the combined form, Khelltron, possesses measurably less toxic effects than khellin and thus may warrant further clinical trial.

The authors emphasize the difficulty of evaluating any continuous favorable influence produced by a drug upon the course of angina pectoris in a particular patient or group of patients. I have been keenly disappointed in my efforts to put any of these drugs to effective use in furthering the continuous control of angina pectoris generally. This attitude may well relate to a tendency to put them to trial only after a well ordered regimen for the individual patient has failed to control satisfactorily the occurrence of his anginal episodes.

Present Status of ACTH and Cortisone in the Management of Cutaneous Diseases

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THE final place of ACTH and cortisone in our therapeutic armamentarium for the management of patients with cutaneous diseases will not be established for many years. Furthermore, as is the case at the present time, there will continue to be divergent points of view among physicians as to the indications and contraindications for the use of this therapeutic modality. However, the experience which has been accumulated by numerous observers since the introduction of these hormones to clinical medicine four years ago[9] makes it possible to adopt certain general principles which serve as a guide in selecting patients for such treatment. The purpose of this paper is to outline our views on the subject. For the most part, this discussion will be based on our personal experience with the use of ACTH and cortisone in the management of patients with cutaneous diseases who were referred to the Dermatology Department of the John Sealy Hospital or to the private office of one of us (CSL).

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Some of the cortisone used in this study was supplied by the Upjohn Company and by Merck and Company, Incorporated.
Read before the Texas Dermatological Society, Houston, April 26, 1953.

PHYSIOLOGIC CONSIDERATIONS

Despite the fact that there is a difference in the physiologic action of ACTH and cortisone, the ultimate hormonal effects of the administration of either steroid are essentially the same. It is well known that a balance exists between the anterior pituitary gland and the adrenal cortex, and it is because of this relationship that the clinical effects of the two hormones are similar. Treatment with ACTH leads to decreased activity of the pituitary, and the administration of cor-

tisone results in suppression of adrenocortical function. Excessive dosage or prolonged cortisone therapy tends to cause atrophy of the adrenal cortex. An abrupt withdrawal of these drugs results in a period of deficiency of endogenous ACTH and adrenocortical steroids. Clinically this insufficiency is evidenced by weakness, malaise, fatigability, hypotension, and even death.[6] This suppression of the natural activity of the pituitary gland and adrenal cortex is more evident following rapid reduction of dosage or withdrawal of cortisone than by a similar withdrawal of ACTH; it is even more evident when cortisone has been given by the oral route.

The administration of large doses of cortisone to patients with intact adrenal glands results in retention of sodium and water and an increase in the excretion of potassium. With continued use of the hormone, this retention usually tends to decrease. However, in older patients (especially if there is decreased cardiac reserve or impaired renal function), a rapid gain in weight indicating fluid retention frequently becomes evident, and discontinuation of the drugs and/or the use of diuretics may be essential.

Extensive loss of nitrogen, even to the extent of producing a negative nitrogen balance, is another physiologic side effect of prolonged cortisone therapy.[13] Osteoporosis due to interference with protein metabolism of osteoid tissue with resultant loss of calcium and phosphorus is an untoward result which has become more apparent, especially in elderly patients receiving long-term maintenance therapy,[17] following the increased use of these hormones.

Cortisone stimulates glyconeogenesis from protein and fat and also inhibits some phases of carbohydrate utilization. In normal persons, this diabetogenic action is well tolerated by the functional activity of the pancreatic islands, and there has been no evidence of permanently induced diabetes through the action of these hormones.[13, 22] However, incipient diabetes may become manifest during cortisone treatment, and known diabetic patients require an increased amount of insulin for maintenance.

In some patients, there is a tendency for cortisone and ACTH to cause elevation of blood pressure above preexisting levels. However, this is uncommon except in patients with cardiovascular or renal disease.

The development of gastric or duodenal ulcers or the aggravation of existing ulcers in patients under treatment with cortisone and ACTH has been reported by numerous observers.[7, 11] This is brought about probably by the stimulating effect of cortisone on the gastric mucosa which results in the increased production of both hydrochloric acid and pepsin.

Cushing's syndrome, with characteristic fat distribution, rounded face, hirsutism, acneiform eruptions, buffalo hump, and violaceous striae, is manifested at least in part by the majority of patients on prolonged ACTH or cortisone therapy.

The effects of ACTH and cortisone on the skin have been studied by numerous investigators.[14, 16] These results include generalized thinning of the epidermis, increase in hair growth in the sexual areas and on the extremities, increase in skin temperature, stimulation of the sweat glands, reduction of activity of the sebaceous glands, development of telangiectasia, and appearance of acneiform lesions. Often, the suppressive action of the hormones on the acute inflammatory lesions of the skin is accompanied by local deposition of pigment. In contrast to ACTH, prolonged treatment with cortisone does not tend to produce a generalized increase in pigmentation of the skin.[19]

There is a decrease in the number of circulating eosinophils and lymphocytes following administration of ACTH and cortisone. This eosinophenic effect has been studied by many investigators,[15] and it is the basis of a laboratory test that is a sensitive indicator of the efficacy of cortisone and ACTH therapy in a given patient. Because of stimulation of the bone marrow, the administration of these hormones tends to produce a moderate neutrophilia and also a significant reticulocytosis. Their effect on blood platelets and coagulation of the blood continues to be a controversial matter.[19]

In his original report, Hench[9] stressed the suppressive action of ACTH and cortisone on the process of inflammation; this has been confirmed by numerous investigators. The manifestations of a local inflammatory process, which include leukocytic infiltration, phagocytosis, and capillary permeability and exudation, are diminished. In addition, there is an interference with the localization and reparative processes of fibroplasia and deposition of reticulum. Systemically, this suppressive effect is manifested by reduction of fever, increase in appetite, and a general feeling of well-being.

In a recent article, Thorn and others[19] stated that the probable action of these hormones on the hypersensitive state is fundamentally similar to their effect on the inflammatory response of connective tissue. Their observations indicate that it is probable that the common factor in the multiple actions of cortisone and ACTH on the bodily mechanism of defense is a modification of the reactivity of mesenchymal tissue.

Not uncommonly, mental symptoms ranging from minor euphoria or irritability to the major psychotic state are observed during steroid treatment.[3] It now seems probable that these psychic disturbances represent intensification of preexisting personality disorders. Furthermore, epileptiform seizures have been reported to occur during intensive cortisone therapy.[1]

CONTRAINDICATIONS FOR THERAPY

Certain important considerations and studies primarily determined by a careful history and physical examination should be carried out in all patients who are to receive ACTH or cortisone therapy. In particular, this is true if long-term treatment is anticipated.

It is well known that the administration of these hormones may result in activation of latent tuberculosis or lead to increased severity of involvement. For this reason it is most important to rule out this condition, and if there is the slightest suggestion of tuberculosis manifested either by the history or by physical examination, a chest roentgenogram is mandatory. Active tuberculosis is an absolute contraindication to the use of these hormones. The presence of inactive lesions necessitates frequent observation and periodic roentgen-ray examinations of the chest throughout the duration of treatment.

Routine examination of the urine for glycosuria should be made in all patients. The presence of diabetes or a family history of diabetes does not make it mandatory to withhold ACTH and cortisone, but it is essential that periodic blood sugar determinations be done under these circumstances. As noted previously, if it is essential to give the steroid hormones to patients with known diabetes, additional insulin may be required.

Another important contraindication is an active peptic ulcer. Careful evaluation of the patient is in order if there is a history of peptic ulcer, and a roentgen-ray examination of the upper gastrointestinal tract must be done in many patients prior to treatment.

In general, patients with cardiovascular or renal disease or both should not be treated with ACTH or cortisone unless such therapy is apt to be life-saving (for example, in the case of a patient with pemphigus or acute disseminated lupus erythematosus). If steroid treatment is mandatory under these circumstances, the patient must have careful daily observation. This should include frequent blood pressure readings, weight recordings, and observation for evidence of early heart failure.

Elderly patients or persons long immobilized must be watched for the development of osteoporosis, which may result in pathologic fractures. A high protein diet and small doses of testosterone minimize this side effect.[18]

Vascular complications, including thrombosis, embolism, and purpura, occurring in patients on steroid therapy are not seen infrequently. The presence of chronic liver disease seems to predispose to these complications.[20]

Another contraindication is the presence of emotional instability and, indeed, any evidence of a psychiatric disturbance, because it is these patients who are apt to develop neuropsychiatric complications following either short-term or maintenance steroid therapy.

The patient must be observed for evidence of intercurrent infections because symptoms may be masked or suppressed by steroid therapy. In many patients, the concomitant administration of appropriate antibiotic drugs and the hormones is in order.

It cannot be overemphasized that the physician is obliged to consider each patient individually. If the disease is a potentially fatal one (pemphigus, acute disseminated lupus erythematosus, or a severe drug sensitivity reaction), administration of ACTH and cortisone is indicated and indeed mandatory even if there is a distinct contraindication (for example, hypertensive cardiovascular disease, probable peptic ulcer, possible psychosis). On the other hand, if the patient in question has a disease which is nonfatal, such as a dermatitis of some type or a drug sensitivity reaction which may be troublesome and distressing but not alarming, the physician is not justified in accepting the possibility of any type of complication by therapy, even if the disease may be presumed to be transient and of little consequence (for example, temporary hypertension and slight fluid retention).

SELECTION OF PATIENTS FOR THERAPY

In an excellent summary article on this subject, Sulzberger and Baer[14] have prepared lists of "dermatoses in which ACTH and cortisone are frequently or always highly effective as morbidistatic agents," "dermatoses in which ACTH and cortisone are sometimes beneficial," and "dermatoses in which ACTH and cortisone are usually ineffective."

In the first list (usually favorable therapeutic results) they included atopic dermatitis, allergic eczematous contact dermatitis, exfoliative erythroderma, acute and subacute disseminated lupus erythematosus, pemphigus of all types, acute urticaria and angioneurotic edema, multiform erythemas, nummular eczema, eczematous eruptions of the hands, the so-called Sulzberger-Garbe syndrome, and impetigo herpetiformis.

In their second list (therapeutic results sometimes favorable) they included the cutaneous manifestations of chronic lymphatic leukemia and other lymphomas, sarcoidosis, pruritus of unknown cause such as pruritus ani and pruritus vulvae, seborrheic dermatitis, postherpetic neuralgias, lichen simplex chronicus, chronic discoid lupus erythematosus, alopecia areata, scleroderma, dermatomyositis, chronic urticaria, psoriasis, beryllium granuloma, and thrombocytopenic purpura.

Their third list (usually ineffective) included the cutaneous lesions of acute and chronic myeloid leukemia, dermatitis herpetiformis, Kaposi's sarcoma, cancer of the skin, pyodermas, infestations, chronic torpid psoriasis, lichen planus, fungus infections, fixed drug eruptions, and acneiform drug eruptions.

They indicated that ACTH and cortisone are effective only for drug sensitivity reactions which are identical morphologically with erythema multiforme, urticaria, eczematous dermatitis, exfoliative dermatitis, and angioneurotic edema.

To some extent, this information is similar to that which is distributed by the pharmaceutical companies which manufacture these hormones. Sulzberger and Baer emphasized that for the most part their statements regarding the efficacy of ACTH and cortisone were based on their own personal experience although in some cases they depended on the reports of other observers.

Essentially, our own experience is not at variance with that recorded by these authors or by other observers. However, we are of the opinion that lists of diseases in which these hormones are effective or partially effective, such as those which have been cited, tend to be misleading in that it is implied that persons with these conditions should be treated with either ACTH or cortisone or both. The physician who is not a dermatologist is apt to overemphasize the use of these hormones if he is guided by this information.

For example, all dermatologists will agree that ACTH and cortisone suppress both the objective and subjective manifestations of atopic dermatitis in the majority of patients (infants, children and adults), but few will agree that such therapy should be instituted for these patients except in the case of a small number of selected individuals. We believe that treatment with ACTH and cortisone has a distinct place in our therapeutic armamentarium for the management of severe, extensive contact dermatitis, but certainly such therapy should not be instituted for the vast majority of patients who have self-limited, localized contact dermatitis, despite the fact that the duration of involvement might be decreased significantly.

The inclusion in these lists of psoriasis, alopecia areata, chronic urticaria, seborrheic dermatitis, pruritus ani, pruritus vulvae, nummular ezcema, and eczematous eruptions of the hands seems to indicate that this treatment is recommended for these conditions, or at least for a significant percentage of patients affected with these dermatoses. Certainly this is the impression which is conveyed to the physician who is not a dermatologist. It seems justifiable to state emphatically that these hormones should not be used for the treatment of any of these diseases except perhaps in a few selected cases.

With these considerations in mind, we have concluded from our own experience that ACTH and/or cortisone therapy is indicated for almost all patients who have the following skin diseases: pemphigus of all types; acute disseminated lupus erythematosus; exfoliative dermatitis (generalized erythroderma); severe drug sensitivity reactions; and severe extensive contact dermatitis. The administration of ACTH and/or cortisone is mandatory for patients with acute disseminated lupus erythematosus, severe pemphigus, exfoliative dermatitis, and severe, potentially fatal drug sensitivity reactions, especially cutaneous sensitivity manifestations accompanied by systemic involvement, such as blood dyscrasias, for these patients, one is justified in risking almost any type of complication of therapy, including the activation of tuberculosis. However, it is not justifiable to accept the risk of a possible complication suggested by the history, physical examination, or laboratory tests if the patient has severe extensive contact dermatitis.

Prolonged maintenance therapy for an indefinite period is necessary for patients with acute disseminated lupus erythematosus. Patients who have pemphigus require maintenance treatment for variable periods of time. Usually short-term therapy is involved in the treatment of patients with severe contact dermatitis and drug sensitivity reactions.

We are of the opinion that steroid therapy is indicated for a selected group of patients who have the following diseases: erythema multiforme; subacute disseminated lupus erythematosus; severe acute urticaria and/or angioneurotic edema providing other therapeutic measures are ineffective; and eczematous "id" eruptions.

The decision in regard to the administration of either ACTH or cortisone or both for a patient who has one of these diseases must be individualized in each case. The physician should be guided by the severity of the disease, the evaluation of the patient as a "possible complication risk," and the response, or rather the lack of response, to other therapeutic measures. For example, a person with severe erythema multiforme may be incapacitated completely and extremely uncomfortable, in which case steroid treatment would be indicated if there are no contraindications. On the other hand, another patient with a few nonincapacitating lesions of erythema multiforme should not have such treatment.

Finally, our experience leads us to believe that there is a third group of diseases for which these hormones are indicated in a very small percentage of selected patients. These dermatoses are as follows: atopic dermatitis; nummular eczema; eczematous eruptions of

the hands; pruritus ani; sarcoidosis; pruritus vulvae; and psoriasis accompanied by arthritis.

We believe that considerable judgment must be exercised in the selection for steroid therapy of patients who have any of the diseases just cited. This decision should be made only by a physician who has special training and experience in dermatology. We have observed patients with atopic dermatitis who have seemed to benefit from short-term cortisone treatment, and we believe that maintenance therapy for months is in order for a few patients with severe atopic dermatitis. We have been disappointed with the long-term clinical results of ACTH for patients with various types of eczematous eruptions, including nummular eczema, eczematous eruptions of the hands, eyelid dermatitis, and eczematous otitis externa, although many such patients have had temporary suppression of their disease. Our experience indicates that steroid therapy does not have a prominent place in the management of the dermatoses just enumerated. It is important to emphasize that it is essential to carry out concomitant therapeutic measures. For example, if it is possible to bring about temporary relief of symptoms of pruritus ani and at the same time investigate the multiple etiologic factors which might be involved and correct them, such treatment might be justified for selected patients.

We do not agree that ACTH and/or cortisone should be used in the management of alopecia areata, seborrheic dermatitis, chronic urticaria, lichen simplex chronicus, and chronic discoid lupus erythematosus except under unusual circumstances.

DOSAGE AND ADMINISTRATION

Recommendations for specific dosages of ACTH and cortisone cannot be made because of variations in the response of different patients with the same disease. Often, during the course of the disease, doses for the same patient must be changed from day to day. In general, the goal to be achieved is the suppression of the acute manifestations of the disease as quickly as possible—this to be followed by reduction of the dosage to a minimum maintenance level, and if indicated, gradual withdrawal of the drug. It should be kept in mind that the exact mechanisms by which these hormones produce their favorable effects are not known; that their action is suppressive and not curative; that the etiologic factors are not removed; and that, in the final analysis, the eventual outcome depends upon the natural course of the disease in question.

Table 1 gives a brief outline of the differences in the time of action of various preparations of cortisone and ACTH.[20, 21]

It has been reported by a number of observers that certain patients have not responded to intramuscular injections of ACTH but have reacted satisfactorily to the same preparation administered by slow intravenous infusion. This unresponsiveness has been termed "ACTH resistance" by Forsham and others[4] and possibly is due to destruction or inactivation of the hormone by enzymatic action within the muscle. This apparent "resistance" now seems to be of less significance in the use of the newer, more highly purified ACTH preparations.

TABLE 1.—*Difference of Time of Action of Various Cortisone and ACTH Preparations.*

Preparation	Administration	Duration of Single Dose (hr.)	Peak of Activity*	Dosage Schedule
Cortisone acetate suspension	Intramuscular	24†	8-12	At 4-8 hr. intervals at first; then every 24 hr.
Cortisone acetate tablets	Oral	<10	2-4	At 4-6 hr. intervals at first; then every 6-8 hr.
ACTH, aqueous solution	Intramuscular	6-8	4-6	Divided doses every 6 hr.
ACTH‡, long-acting gel	Intramuscular or subcutaneous	24-36	15-18	Every 24 hr.
ACTH, lyophilized powder	Intravenous	8-12	<8	Infusion over 8-10 hr. period

*Measured by decrease in circulating eosinophils.
†After prolonged therapy the cumulative effect may persist several days.
‡ACTH gels now are standardized in terms of commercial or clinical units. A gel preparation labeled as clinically equivalent to 40 USP units actually contains approximately 14 USP units of highly purified ACTH.

Our basic dosage schedules are similar to those reported by others.[8, 10, 12, 15] Usually, cortisone is administered by the oral route. For the majority of patients, the initial dosage is 300 to 400 mg. given in divided doses during the first twenty-four hours and followed by gradual reduction to a maintenance level of 100 mg. or less. In self-limited dermatoses such as acute contact dermatitis, maintenance therapy is not necessary, and consequently the drug is withdrawn gradually during a period of four to fourteen days. In general, patients who require maintenance therapy (acute disseminated lupus erythematosus, exfoliative dermatitis, and pemphigus) are managed more satisfactorily if the dosage of cortisone is not more than 75 mg. daily. It is obvious that long-term therapy (years rather than months) has not been evaluated adequately. Recent reports indicate that there is no need for interrupted courses of cortisone or alter-

nating courses of cortisone and ACTH.* However, all patients receiving protracted treatment must be carefully observed for "break through symptoms" of their disease and especially for situations of stress such as complicating illness or injury; under these circumstances, additional amounts of cortisone are required.

For initial management, we have found that the intravenous use of ACTH is most satisfactory both from a clinical and economic standpoint. The lyophilized powdered ACTH is dissolved in 1,000 cc. of 5 per cent glucose in distilled water and administered by slow intravenous infusion over an eight to ten hour period. The initial dose is usually 25 mg. per day with gradual reduction to 10 mg. or even 5 mg. every twenty-four hours. If feasible, on the fourth or fifth day prior to discharge of the patient from the hospital, therapy is changed from ACTH to orally administered cortisone or ACTH injected intramuscularly (usually the gel preparation). In this instance the initial dose of cortisone is usually 100 mg. per day followed by gradual reduction of dosage if possible.

All patients receiving ACTH or cortisone therapy are placed on a salt free diet (500 mg. or less per twenty-four hours), a high protein diet (80 to 90 mg. per twenty-four hours), and potassium chloride (3 Gm. per twenty-four hours). They must be observed frequently—daily during the first few days of treatment and then at intervals of not less than one week. As previously mentioned, patients on prolonged maintenance treatment also are given testosterone. The dosage of this hormone varies with age and sex.

When anticipated clinical response does not occur, one of several factors should be considered as a possible cause. First, the particular disease may not be responsive to hormonal therapy. We have seen several patients with acute urticaria due to drug sensitivity and acute contact dermatitis who have not improved, either subjectively or objectively, despite the administration of large doses of cortisone. Second, the dosage of the drug administered may not have been large enough for suppression of symptoms. Except for potentially fatal diseases such as acute systemic lupus erythematosus, acute pemphigus, and some severe drug eruptions, we do not believe it is warranted to exceed 400 mg. of cortisone per twenty-four hours for the initial suppressive dosage.

There is also some evidence that diseases which respond initially sometimes appear to become resistant to the hormone and require progressively larger doses and eventually even become entirely refractory to hormonal treatment.

**Usually, we administer 10 to 20 mg. of ACTH every three to five days to patients on maintenance therapy with cortisone.*

SUMMARY

The clinically important physiologic effects of ACTH and cortisone are discussed.

The following minimal evaluation of a patient is essential before the institution of ACTH or cortisone therapy:

1. Complete history and physical examination with emphasis on tuberculosis, peptic ulcer, and cardiovascular, renal, and neuropsychiatric disorders.

2. Chest roentgenogram if indicated by the history or physical examination.

3. Urinalysis.

The indications and contraindications for the use of ACTH and cortisone in treatment of cutaneous diseases are examined and summarized and justification for the use of these hormones in the presence of certain complications is discussed.

The routes of administration and dosage schedules of ACTH and cortisone are briefly described.

It is emphasized that a broad knowledge regarding all aspects of the management of cutaneous diseases is essential if the physician is to use ACTH and/or cortisone appropriately and safely for patients with skin disorders.

REFERENCES

1. Baehr, G., and Soffer, L. J.: Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin, Bull. New York Acad. Med. *26:*229-234 (April) 1950.

2. Omitted on proof.

3. Clark, L. D.; Bauer, W.; and Cobb, S.: Preliminary Observations on Mental Disturbances Occurring in Patients Under Therapy with Cortisone and ACTH, New England J. Med. *246:*205-216 (Feb. 7) 1952.

4. Forsham, P. H.; Renold, A. E.; and Frawley, T. F.: Nature of ACTH Resistance, Abstr., J. Clin. Endocrinol. *11:*757 (July) 1951.

5. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G.; and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. *8:*15-66 (Jan.) 1948.

6. Fraser, C. G.; Preuss, F. S.; and Bigford, W. D.: Adrenal Atrophy and Irreversible Shock Associated with Cortisone Therapy, J.A.M.A. *149:*1542-1543 (Aug. 23) 1952.

7. Gray, S. J.; Benson, J. A., Jr.; Spiro, H. M.; and Reifenstein, R. W.: Effects of ACTH and Cortisone upon Stomach: Its Significance in Normal and in Peptic Ulcer, Gastroenterology *19:*658-673 (Dec.) 1951.

8. Haserick, J. R.; Corcoran, A. C.; and Dustan, H.: ACTH and Cortisone in Acute Crisis of Systemic Lupus Erythematosus, J.A.M.A. *146:*643-645 (June 16) 1951.

9. Hench, P. S.; Kendall, E. C.; Slocumb, C. H.; and Polley, H. F.: Effect of Hormone of Adrenal Cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet., Mayo Clin. *24:*181-197 (April 13) 1949.

10. Kierland, R. R.; O'Leary, P. A.; Brunsting, L. A.; and Didcoct, J. W.: Cortisone and Corticotropin (ACTH) in Dermatology, J.A.M.A. *148:*23-26 (Jan. 5) 1952.

11. Kirsner, J. B.; Klotz, A. P.; and Palmer, W. L.: Unfavorable Course of Gastric Ulcer During Administration of ACTH and Cortisone, Gastroenterology *20:*27-29 (Jan.) 1952.

12. Lever, W. F.: ACTH and Cortisone in Diseases of Skin, New England J. Med. *245:*359-363 (Sept. 6) 1951.

13. Sprague, R. G., and others: Observations on Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. *85:*199-258 (Feb.) 1950.

14. Sulzberger, M. B., and Baer, R. L.: Present Status of ACTH, Cortisone and Compound F in Dermatologic Management; Guide

for General Practitioner, 1952 Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, 1953, pp. 7-8.

15. Sulzberger, M. B.; Witten, V. H.; and Yaffe, S. N.: Cortisone Acetate Administered Orally in Dermatologic Therapy, A.M.A. Arch. Dermat. & Syph. *64*:573-579 (Nov.) 1951.

16. Sulzberger, M. B.; Sauer, G. C.; Herrmann, F.; Baer, R. L.; and Milberg, I. L.: Effects of ACTH and Cortisone on Certain Diseases and Physiologic Functions of Skin: I. Effects of ACTH, J. Invest. Dermat. *16*:323-337 (May) 1951.

17. Teicher, R., and Nelson, C. T.: Osteoporosis and Pathological Fractures Following Treatment with ACTH and Cortisone, J. Invest. Dermat. *19*:205-210 (Sept.) 1952.

18. Thorn, G. W., and others: Pharmacologic Aspects of Adrenocortical Steroids and ACTH in Man, New England J. Med. *248*: 284-294 (Feb. 12) 1953.

19. Ibid. *248*:323-337 (Feb. 19) 1953.

20. Ibid. *248*:369-378 (Feb. 26) 1953.

21. Ibid. *248*:588-601 (April 2) 1953.

22. Wilson, D. L.; Frawley, T. F.; Forsham, P. H.; and Thorn, G. W.: Functional Relationship Between Pancreatic Islets and Adrenal Cortex in Man, Proc. Am. Diabetes A. *10*:25-34, 1950.

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ABSTRACT OF DISCUSSION

DR. EVERETT R. SEALE, Houston. This is an excellent, conservative, and well thought out paper, and certainly the subject has been well covered. I am in hearty agreement with the basic premises presented by the essayists, namely, steroids should be used as a life-saving procedure in acute lupus erythematosus and pemphigus and to alleviate symptoms in severe, acute, self-limited diseases. They are also of value in the more prolonged but still self-limited dermatoses such as exfoliative dermatitis resulting from gold sensitivity. Their use in such conditions as atopic dermatitis, nummular eczema, and pruritus ani et vulvae should be the exception, not the rule. The relief afforded patients with the latter group of diseases while on steroid therapy is so great that they may rebel upon its withdrawal. Certainly it is easier to start therapy than to stop it.

The danger of cortisone and ACTH has been impressed upon me in two cases. In one case a woman with acute lupus erythematosus became psychotic upon the third day of therapy. Another, with severe penicillin urticaria, developed paroxysmal tachycardia on the second day of therapy. If either of these patients had been receiving steroids for poison ivy dermatitis, it would have been difficult for me to justify their usage.

Porphyrin Metabolism and the Cutaneous Manifestations of Porphyria

A REVIEW

EUGENE P. SCHOCH, JR., M.D., Austin, Texas

PORPHYRINS are relatively obscure chemical compounds which are fundamentally integrated with all cellular metabolism. These compounds are ubiquitous, yet relatively little is known of their structure and function physiologically or in disease. It is the purpose of this paper to review briefly some facts about normal porphyrin metabolism and the dermatologic aspects of certain porphyric conditions.

HISTORY

In 1871 Hoppe-Seyler prepared in vitro the first known porphyrin.[16] It was called hematoporphyrin because it was thought to be the naturally occurring pigment of the hemoglobin molecule. All porphyrins isolated from urine and feces in a variety of conditions were subsequently called hematoporphyrins.

This erroneous belief prevailed for years because early analytic methods (spectroscopic) were not sufficiently sensitive to delineate this artificially prepared compound from the natural porphyrins: coproporphyrin, uroporphyrin, and protoporphyrin. This distinction was made in 1913 by Fischer,[9, 10] who eventually was able to synthesize protoporphyrin and show it to be the true porphyrin of hemoglobin.[11] This porphyrin is also the constituent of other iron porphyrin enzymes of the respiratory type, such as catalase, cytochrome, and myoglobin. As a magnesium complex it comprises the nucleus of one of nature's most abundant substances—chlorophyll.

Read before the Texas Dermatological Society, Houston, April 26, 1953.

CHEMISTRY AND PHYSIOLOGY

Basically all porphyrins are similar in their structure, which extends from a skeleton of four pyrrole nuclei connected by four methene groups (a porphin) (fig. 1).

The type of porphyrin is determined by the substituent groups attached to the eight free corner carbon atoms of the pyrrole nuclei as shown in table 1.

TABLE 1.—*Substituent Chemical Groups Attached to the Free Corners of the Porphin Nucleus of Three Porphyrins.*

Porphyrin	Substituent Groups	Theoretical Number of Possible Isomers
Coproporphyrin	4 methyl 4 proprionic	4
Uroporphyrin	4 acetic 4 proprionic	4
Protoporphyrin	4 methyl 2 proprionic 2 vinyl	15

Porphyrins are thought to arise in the bone marrow (hemoglobin synthesis), liver, and central nervous system.[17] In the production of hemin (protoporphyrin)

coproporphyrin is a normal side product and is excreted normally in the urine in the range of 50 to 300 gammas per twenty-four hours. Of this amount 60 to 80 per cent is coproporphyrin I. Certain disease states will cause an increase in coproporphyrin excretion.

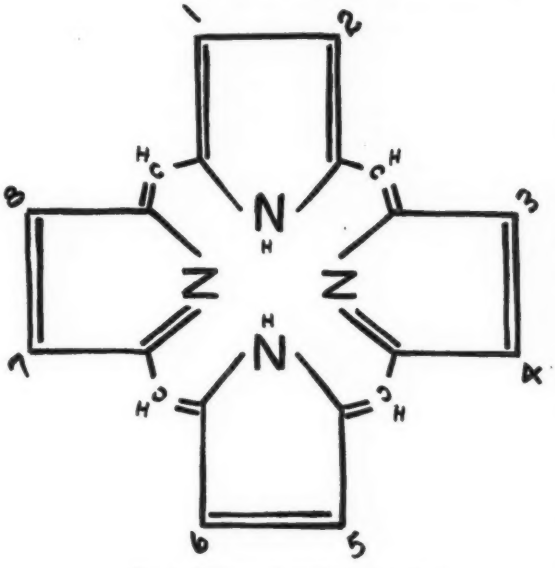

FIG. 1. Structure of porphyrin (porphin).

Among these are jaundice, cirrhosis, hepatitis, lymphoblastoma, poliomyelitis, heavy metal poisoning, certain anemias, Hodgkin's disease, and porphyria.

Uroporphyrin does not appear normally in the urine. It is present primarily in cases of porphyria; however, it may rarely be secondary to some other systemic diseases.[17]

There are colorless precursors or chromogens of the porphyrins (coproporphyrinogen and uroporphyrinogen) which may be converted to the colored porphyrin by light, heat, air, and chemical oxidizers.

Porphobilinogen is the chromogen of porphobilin, a dark red-brown to black pigment which may contribute to the color of the urine in porphyria. Its presence is not pathognomonic but is highly suggestive of porphyria.

TESTS

There are a number of tests for determining the presence of porphyrins.

1. All porphyrins fluoresce with near ultraviolet light [4,000 angstrom units (Watson[22]); 3,300-4,300 angstrom units (Blum and Pace[1])]. The basic principles of separating and identifying different types of porphyrins lie in their specific spectroscopic and solubility characteristics; however, their stero-isomers can be identified only by determination of the melting points of their respective methyl esters.

2. Quantitative determination of coproporphyrin and uroporphyrin may be made by a process of ether and butyl alcohol extraction and comparison of the fluorescence of the fractions to that of known standard solutions. This may be shown diagrammatically as in figure 2.

3. A simple rough test has been described by Dillaha and Hicklin.[7] They merely dilute a small quantity of urine with 1.5 normal hydrochloric acid to at least twenty times its original volume and measure its fluorescence as a uroporphyrin solution. This test compares favorably with the more tedious analytic procedures, but it gives only the combined total porphyrin value (coproporphyrin plus uroporphyrin).

4. Porphobilinogen is easily determined by the Watson-Schwartz modification of Ehrlich's urobilinogen test[23] (fig. 3).

PORPHYRIA

Porphyria is a rare, familial inborn error of metabolism.[12] It is a disease entity which is characterized

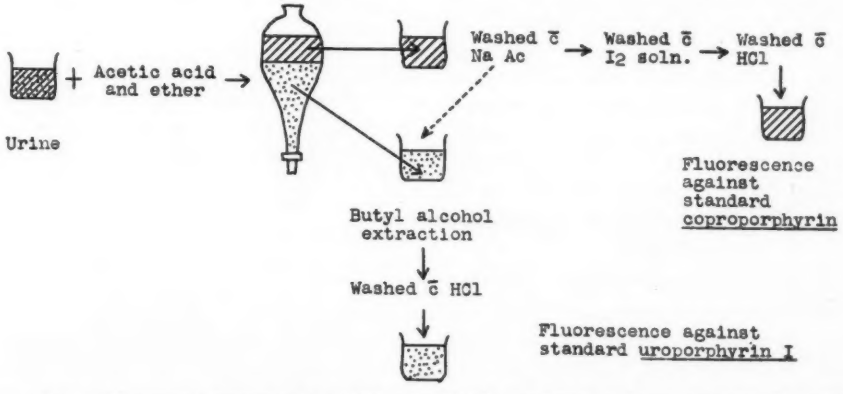

FIG. 2. Diagrammatic presentation of Dillaha and Hicklin's modification of Schwartz's ether-butyl alcohol analytic procedure for quantitative determination of coproporphyrin and uroporphyrin.

by a variety of symptoms and signs and by the presence of abnormal kinds and amounts of porphyrins, especially uroporphyrin, in the urine. Dillaha[7] has cautioned that porphyria should not be confused with porphyrinuria, which at times has been used synonymously but actually means merely a condition of increased excretion of porphyrin (coproporphyrin) in the urine.

Clinically and chemically there are three types of porphyria. A summary of their systemic features is shown in table 2.

and hair may develop even to the extent of red hair turning black. Melanosis may be spotted as pigmented macules on exposed surfaces only. The facies may be dusty and bluish-red with injected conjunctivae giving a dissipated appearance. Some, especially women, develop marked hirsuitism; others merely a generalized pruritus.

Occasionally the skin of the face and neck have the appearance of colloid degeneration; other patients may develop milia. The histologic findings in Brunsting's cases showed a homogenous, colloid-like substance in the papillary cutis in some and a nonspecific dermatitis in others.[3, 5] Bolgert, LeSourd, Canivert, and

TABLE 2.—*Classification and Main Features of Porphyria.*

	Type	Sex	Photosensitivity	Neurologic Manifestations	Special Features	Uroporphyrin	Coproporphyrin	Porphobilinogen	Origin of Porphyrin
I.	Photosensitive (congenital, infantile) "erythropoietica" Rare	Male	Early		Erythrodontia Splenomegaly Hemolytic anemia	I	I	—	Bone marrow
II.	Intermittent acute (toxic) Relatively common	Female		Hysteric or psychotic behavior Neuropathies with pain Paralysis Death due to respiratory paralysis	Abdominal pain	Zinc complex Waldenström	III	+	?
III.	Mixed (chronic, cutanea tarda) "hepatic" Relatively uncommon	Male (?)	Adult life (less severe)	Infrequent	Jaundice Liver damage or cirrhosis frequent	Zinc complex Waldenström or I	I & III	+ —	Liver

Modified from Watson, C. J.: Some Recent Studies of Porphyrin Metabolism and Porphyria, Lancet *1*:541 (March 10) 1951.

The cutaneous picture in porphyria may be quite varied. In the photosensitive type the manifestations are often those of an acute hydroa with severe vesiculation, scarring, and mutilation.

With the acute intermittent type patients may have hyperpigmentation of the skin; however, there are no other characteristic findings.

Detailed studies of the dermatologic features of the "mixed" type were made by Brunsting.[3, 5] He described blistering of the dorsal surface of the hands following exposure to light, heat, or trauma as a prominent initial manifestation. A diffuse melanosis of the skin

Habib found vesicles containing few cells and no eosinophils, and having a hairy and frayed appearing base.[2]

Other dermatologic entities or symptom complexes have been reported in association with porphyria. Among these are some cases of hydroa vacciniforme and estivale,[14] epidermolysis bullosa,[14] lupus erythematosus,[6, 14] dermatomyositis,[6, 14] xeroderma pigmentosum,[14] erythema multiforme bullosa,[14] scleroderma, psoriasis,[6] calcinosis,[21] keloid formation,[21] arsenical dermatitis,[4, 18] leukemia cutis,[4] erythema induratum,[4] scrofuloderma,[4] and exfoliative dermatitis of Hodg-

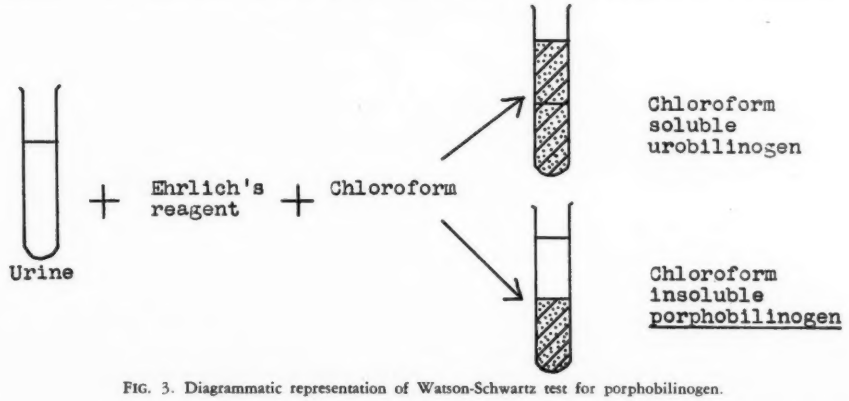

FIG. 3. Diagrammatic representation of Watson-Schwartz test for porphobilinogen.

kin's disease.[4] Ebert,[8] however, pointedly stated that there is no evidence of true porphyria in cases of ordinary light sensitivity including many of those listed above. Others[4, 24] agree with this viewpoint and indicate that many such reports were probably describing only secondary porphyrinuria with the dermatoses, not true porphyria.

Although Meyer-Betz was able to photosensitize himself by the autoinjection of hematoporphyrin[19] the exact photodynamic effect of natural porphyrins has not been established. There is no definite or consistent correlation between porphyrin excretion and photosensitivity.[5, 14, 24] Experimental exposure of porphyric patients to sunlight or to artificial ultraviolet light usually causes no blistering. Brunsting[5] postulated the possible need for repeated exposures to light in order to bring about the cutaneous picture present in some cases of porphyria (fig. 4).

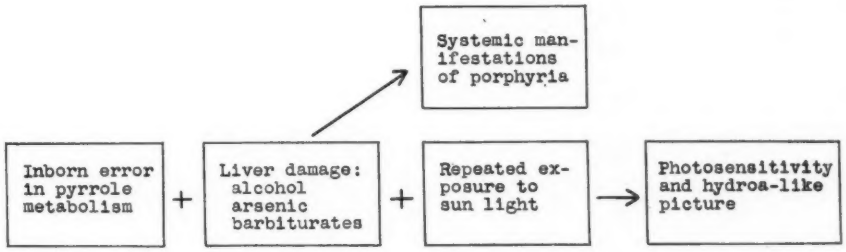

FIG. 4. Possible pathogenesis of chronic (mixed) type of porphyria.

In general, therapy in all types of porphyria has been unsatisfactory. In the light sensitive types protection from ultraviolet light and trauma is merely symptomatic but often expedient for the partial control of the skin manifestations. Splenectomy may cause remission of light sensitivity in the congenital type.[22]

In the chronic, mixed (or hepatic) type therapy should be directed toward control of the liver damage, that is, avoidance of hepatotoxic substances (especially alcohol) and routine anticirrhotic regimens. Recently Dillaha and Hicklin treated such cases with vitamin B_{12}. One patient was thought to be benefited by the vitamin; however, they emphasized that abstinence from all alcohol was absolutely essential. Watson similarly was not impressed by the response in one series of cases treated with vitamin B_{12} alone.[15] Niacin and nicotinic acid apparently helped some cases of Obaneja,[14] riboflavin improved some cases of Stick,[24] and cortisone caused decrease in excretion of porphyrin in the case of Gilbert, Toupin, and Bell[13] but did not alter the fatal outcome.

DISCUSSION

From a dermatologic point of view it would behoove us to consider the possibility of porphyria in patients presenting cutaneous signs of photosensitivity with or without bullae, vulnerability to slight trauma, atypical pigmentation, hirsuitism and even pruritus. Strictly speaking such a diagnosis is not so simple to make as Zeligman indicated.[25] He suggested that urines in suspected cases merely be subjected to examination for fluorescence under an ordinary office Wood's light. This, however, would identify only a certain group as being porphyrinuric. Uroporphyrin itself must be identified to substantiate the diagnosis of porphyria. The simple Wood's light test would be false-negative should only the colorless chromogens be present. Part of this error may be obviated by either letting the urine stand exposed to the light and air for a period of time, boiling it, or artificially oxidizing the chromogen by chemicals (for example, iodine). The Wood's light test would be false-positive (for porphyria) should porphyrins other than uroporphyrin give rise to the red fluorescence (for example, in any number of previously mentioned toxic conditions and even in the rare cases of idiopathic coproporphyrinuria). Only true extractions and/or spectrographic analyses would prove the diagnosis of porphyria. The presence of porphobilinogen would corroborate the diagnosis; however, this finding is often absent when there are no gastrointestinal or neurologic symptoms present.

After the diagnosis has been made, integrated management with an internist would be indicated to include tests of liver function and therapy directed at improving any liver damage should it be present.

SUMMARY

A brief review of porphyrin metabolism is made to emphasize a few basic facts in its history, chemistry, origin, and physiology.

Three types of laboratory tests to determine the presence of porphyrins and porphobilinogen are reviewed.

The general features, cutaneous manifestations and treatment of porphyria are summarized.

The practical implications of porphyrin studies to the practitioner are discussed.

REFERENCES

1. Blum, H. F., and Pace, N.: Studies of Photosensitization by Porphyrins, Brit. J. Dermat. *49:*465-485 (Nov.) 1937
2. Bolgert, M.: LeSourd, M.; Canivet, J.; and Habib, G.: Porphyrie Congénitale á Révélation Tardive, Bull. Soc. Med. Hôp. Paris, *67:*31-32 (1339-1345) (Nov. 23-30) 1951.
3. Brunsting, L. A., and Mason, H. L.: Porphyria with Cutaneous Manifestations, Arch. Dermat. & Syph. *60:*66-81 (July) 1949.
4. Brunsting, L. A.; Brugsch, J. T.; and O'Leary, P. A.: Quantitative Investigation of Porphyrin Metabolism in Diseases of Skin, Arch. Dermat. & Syph. *39:*294-307 (Feb.) 1939.
5. Brunsting, L. A.; Mason, H. L.; and Aldrich, R. A.: Adult Form of Chronic Porphyria with Cutaneous Manifestations; Report of 17 Additional Cases, J.A.M.A. *146:*1207-1212 (July 28) 1951.
6. Cornbleet, T.: Discussion of Dillaha and Hicklin[7].
7. Dillaha, C. J., and Hicklin, W.: Experimental Therapy of Chronic Porphyria with Vitamin B_{12}, J. Invest. Dermat. *19:*489-497 (Dec.) 1952.
8. Ebert, M.: Discussion of Brunsting[4].
9. Fischer, H.: Ueber das Urinporphyrin, Ztschr. f. physiol. Chem. Strassb., *95:*34-60, 1915.
10. Fischer, H.: Ueber das Kotporphyrin, Ztschr. f. physiol. Chem. Strassb. *96:*148-182, 1915.
11. Fischer, H., and Zeile, K.: Synthese des Hämatoporphyrins, Protroporphyrins und Hämins, Ann. der Chem. *468:*98, 1929.
12. Garrod, A. E: Inborn Errors of Metabolism, ed. 2, London, Henry Fronde, 1923.
13. Gilbert, J. A. L.; Toupin, H. M.; and Bell, R. E.: Acute Porphyria, Canad. M.A.J. *65:*585-587 (Dec.) 1951.
14. Gomez, Orbaneja, J., and Castro-Mendoza, H. J.: Dermatosen und Porphyrie, Dermatologica *94:*327-333, 1947.
15. Gray, C. H., and Neuberger, A.: Effect of Splenectomy in Case of Congenital Porphyria, Lancet *1:*851-854 (April 26) 1952.
16. Günther, H.: Die Hämatoporphyrine, Dtsch. Arch. f. klin. Med. *105:*89, 1911.
17. Lowry, P. T.; Schmid, R.; Hawkinson, V. E.; Schwartz, S.; and Watson, C. J.: Porphyria: Clinical Manifestations in Relation to Chemical Findings, Bull. U. of Minn. Hosp. *27:*97-110 (Nov. 17) 1950.
18. McFarland, A. R., and Strain, W. H.: Significance of Porphyrin Content of Urine in Dermatoses Associated with Sensitivity to Light, Arch. Dermat. & Syph. *38:*727-736 (Nov.) 1938.
19. Meyer-Betz, F.: Untersuchungen über die biologische (photodynamische) Wirkung des Hämatoporphyrins und anderer Derivate des Biut- und Gallenfarbstoffes, Deutsches Arch. f. klin. Med. Leipz. *112:*476-503, 1913.
20. Stich, W.: Die Vitamintherapie der Porphyrinkrankheiten, Deutsche med. Wchnschr. *76:*967-970 (Aug. 3) 1951.
21. Sutton, R. L., and Sutton, R. L., Jr.: Handbook of Diseases of the Skin, St. Louis, C. V. Mosby Co., 1949.
22. Watson, C. J.: Some Recent Studies of Porphyrin Metabolism and Porphyria, Lancet *1:*539-543 (March 10) 1951.
23. Watson, C. J., and Schwartz, S.: Simple Test for Urinary Porphobilinogen, Proc. Soc. Exper. Biol. & Med. *47:*393-394 (June) 1941.
24. Zeligman, I.: Urinary Excretion of Porphyrin in Dermatoses, Arch. Dermat. & Syph. *54:*281-291 (Sept.) 1946; correction *54:* 772 (Dec.) 1946.
25. Zeligman, I.: Red Fluorescence of Urine in Wood's Light as Aid in Office Diagnosis of Porphyria, Arch. Dermat. & Syph. *61:* 853-854 (May) 1950.

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ABSTRACT OF DISCUSSION

DR. C. F. LEHMANN, San Antonio: Dr Schoch has described the chemistry and listed the clinical manifestations of porphyria succinctly, and completely. So my discussion can only dilate upon what he has mentioned.

I would emphasize the following facts which he tells us:

1. The test of Dillaha and Hicklin is simple, but it does not separate uroporphyrin and coproporphyrin.
2. All porphyrins are photodynamic.
3. The mechanism of photosensitivity is unknown.
4. The occasional reports of porphyria in the miscellaneous group of skin diseases are of no significance.
5. All so-called summer eruptions are not porphyria.

The classification of porphyria has not been the same by all writers. One classification* is to divide the condition into congenital (chronic) and acute. The acute then is divided into idiopathic and toxic. The idiopathic finally is divided into manifest and latent.

Some writers ascribe the toxic as due to certain drugs, notably sulfonamides, Sulfonal, Trional, Veronal, and hepatoxic agents such as alcohol, barbiturates, arsenic, and lead.

Brunsting[3] classifies porphyria into three types: congenital, acute, and intermediate or chronic, and has stated that "little is known concerning the factors that precipitate acute porphyria, but in certain cases a damaging influence on the liver either by disease, such as cirrhosis, or by hepatoxic drugs or poisons (alcohol) appear to contribute to the development of the manifest phase of porphyria." This suggests that the so-called toxic state is a latent porphyria that is precipitated into the acute or manifest stage.

The congenital type is of chief interest to dermatologists because of the manifestation of hydroa vacciniforme and discoloration (red or pink) of the teeth. There is itching and burning of the exposed skin surfaces, frequently associated with photophobia and conjunctivitis. There may be a diffuse hyperemia and edema of the face after exposure to sunlight. If uncomplicated, the bullae form a crust and healing occurs with relatively little scarring. If the bullae are secondarily infected, considerable scarring results. Congenital porphyria may leave after puberty. Later in the course of the disease anemia and splenomegaly may develop, and there may be marked deformity of the ears, nose, face, and fingers.

The acute or severe toxic type of porphyria should be of chief interest to the surgeon because of the severe abdominal crisis. It is attended with psychic manifestations which may be insomnia, depression, irritability, hysteric outbursts, hallucinations of visions or hearing, epileptic seizures, and coma. The neurologic manifestations in the acute attack may be paresthesias, varying from vague pains in the extremities to diagnostic flaccid paralysis. These manifestations may suggest a multitude of possibilities. It is interesting to note that in the severe toxic state of porphyria there is no increase of proteins in the spinal fluid.† The severe cramplike abdominal pains in this condition have led to many an exploratory laparotomy, and surgeons should be aware of the condition to avoid unnecessary surgery. Constipation is usually marked, nausea and vomiting usually severe. Fever and leukocytosis may or may not be present. In contrast to the symptoms so typical of an acute surgical condition, when the abdomen is examined, there is no rigidity, the rebound phenomenon is absent and "the tenderness which is generalized is not so marked as would be expected from the complaints."† Hypertension during the attack with a return to normal in a remission is commonly observed. In the presence of severe neurologic symptoms the mortality is from 80 to 90 per cent.

In acute porphyria there may be pigmentation, but other cutaneous manifestations are infrequent. Brunsting listed the changes in chronic porphyria[3] as "melanosis, hypertrichosis, milia and a chemical and physical alteration of the connective tissue, which renders the surface layers susceptible to trauma and gives rise to a blistering reaction to light. Only the exposed skin is so affected, presumably through the toxic influence of accumulative doses of light, although the

*Bauer, E.: Akute Porphyric im Kinderalter, Ann. Paediat. *161:* 193-207 (Sept.-Oct.) 1943.

†Hayman, J. M., Jr.: Porphyria, Ohio State M. J. *45:*800-805 (Aug.) 1949.

blisters cannot well be reproduced by artificial means, and cannot be reproduced at all on the skin that has been protected from light."

MacGregor, Nicholas, and Rimington‡ reported a patient with porphyria whose urine, serum, and blister fluid fluoresced, as did his entire skin, especially scars of old skin lesions that fluoresced a bright red.

The urine in acute porphyria contains various amounts of uroporphyrin I and III besides coproporphyrins. These are all, or nearly all, present as zinc complexes, which would account for the lack of light sensitivity since the metal complexes of the porphyrins are not photosensitive.

The amount of porphyrin in the urine varies considerably from time to time, and with the reaction of urine. At times it is reddish when voided, at other times only darkens on exposure to light. Irrespective of these changes, the urine in acute porphyria, and in those who carry the trait, although symptom-free, nearly always contains another abnormal compound called porphobilinogen.† Porphobilinogen is the colorless precursor of the principal pigments in porphyric urine. It apparently does not occur in the urine of light sensitive type, but in this light sensitive type large amounts of uroporphyrin appear and result in a red urine; whereas, in the intermittent type the urine is darker and more brown in color.§

It seems that large amounts of uroporphyrin and coproporphyrin, the majority of all being in the free state, are essential for photosensitization.†

"Porphyrins possess the power to sensitize the skin to light, but the photodynamic mechanism of this process is obscure. Attempts to reproduce an eruption in the skin of porphyric individuals by exposing them to sun or to artificial light have been, for the most part, unsuccessful."‖

It is important in discussing this subject to mention the fact that "there are many miscellaneous conditions that cause a red urine. Patients taking pyridine or eating red beets may have a pink color in the urine. This may be similarly noted in the alkaline urine of patients taking phenolphthalein, rhubarb, senna, cascara or santonin. Hematuria, hemoglobinuria and myoglobinuria are endogenous causes of red urine."¶

‡MacGregor, A. G.: Nicholas, R. E. H.; and Rimington, C.: Porphyria Cutanea Tarda, A.M.A. Arch. Int. Med. *90*:483-504 (Oct.) 1952.

§Ivers, W. M.: Acute Intermittent Porphyria, J. Urol. *66*:816-818 (Dec.) 1951.

‖Brunsting, L. A., and Mason, H. L.: Porphyria with Cutaneous Manifestations, Proc. Staff Meet., Mayo Clinic *22*:489-494 (Oct. 29) 1947.

¶Goldman, A. M., and Kaplan, M. H.: Acute Porphyria, Ann. Int. Med. *34*:415-427 (Feb.) 1951.

INACTIVATED INFLUENZA VIRUS VACCINE IN THE THERAPY OF HERPES ZOSTER

Clinical Evaluation

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THE etiologic agent of herpes zoster is generally conceded to be a specific virus. Considerable evidence indicates this virus is similar to that of varicella; however, this is a moot question and of only academic importance. It has been demonstrated that vesicle fluid from active herpetic lesions may infect skin grafts on the chorioallantois of chick embryos. Furthermore, elementary bodies have been demonstrated by electron microscopy in the vesicle fluid from herpes zoster vesicles.[6]

Herpes zoster is a systemic and infectious disease. Malaise and sometimes fever precede the characteristic neurologic and cutaneous signs. The disease shows a seasonal variance, being more common in spring and fall. Men show a slightly higher incidence of the infection than women, but the preponderance is not great.

Pathologic changes occur in the ganglia of the posterior roots of the spinal nerves or their cranial analogues. The most frequent finding is an interstitial inflammation of the ganglionic centers and less often a descending neuritis. In some cases a peripheral neuritis without involvement of the ganglia occurs. Degenerative changes have been found in the ganglia of the posterior roots, in the posterior roots, and in the root fibers of the posterior root columns of the cord as well as in the peripheral nerves.[2] Gram-positive cocci found in these areas of inflammation are probably secondary invaders of the primary exudate. This inflammation of the posterior roots and the peripheral nerves is distinguished by unilateral and segmental localization and greater involvement of the posterior root, horn, and dorsal spinal ganglion.

The cutaneous changes are inflammatory and degenerative in the epidermis and the corium, with vesicle formation in the epidermis and often with hemorrhage and necrosis in the corium. The vesicle content is serum, degenerated epithelial cells, fibrin, leukocytes, and red blood corpuscles. The vesicles are intercellular and unilocular—the result of "balloon" degeneration. So-called eosinophilic staining "zoster bodies of Lipschutz" are found within the basophilic nuclei of the balloon cells.

Healing begins while the vesicle is at its height, new epithelial cells growing in from the bottom and sides, gradually walling off the vesicle.[9] The cutaneous

Read before the Texas Dermatological Society, Houston, April 26, 1953.

symptoms which begin in from two to four days after the onset of neurologic signs are noted as a patch of erythema with edema of the skin. The characteristic cluster of vesicles containing clear fluid then appears. Usually discrete in parts, the vesicles may become confluent. There is an associated lymphadenopathy arising from drainage of the affected field.

The vesicles subside in the average case in about a week or ten days, followed by crusting and scabbing, leaving faintly pigmented scars. If secondary infection develops, the lesions become hemorrhagic and pustular, and more extensive residual scarring is the result. Motor disturbances and muscular paralysis have been reported in cases of extensive disease.

Most patients with herpes zoster recover without incident within ten days to three weeks, but in elderly patients and in cases of severe involvement a syndrome of postherpetic neuralgia, which may be quite a troublesome complication, is encountered. Areas primarily affected by this complication are the trunk and ophthalmic division of the trigeminal nerve; ulceration of the cornea is indeed a serious complication. Geniculate zoster paralysis and deafness is also observed.

TREATMENT

The treatment of herpes zoster is directed toward (1) inhibition of the virus, (2) healing of the skin lesions, and (3) amelioration or relief of the neuralgic pain in the area of the affected sensory ganglion.

From the observations of Andrewes[1] there is little doubt that specific antibodies play an important role in immunity to virus infections. However, the biologic mechanism of this immunity is not understood.

Bondurant,[4] reporting in 1951 at the Southern Medical Association, proposed the following method of treatment: Obtain the serum from blood taken during the active phase of the disease, assuming that the blood contains the causative virus of the disease. Inactivate the serum, and inoculate the patient with daily doses of 5 cc. for a course of 6 to 10 doses. Bondurant's theory is to produce immune bodies to combat the active virus early in the course of the disease and prevent the destructive effects of the organism on the affected nerves. His results indicate that early treatment will prevent many of the destructive phases common in this disease.

Finland[8] indicated that there was little effect from the use of Aureomycin or chloramphenicol on the infective virus as compared to placebo controls. It was thought these drugs did prevent secondary infection. Postherpetic pain of one month or longer was present in 18 per cent of his cases.

Dennie[5] reported commendable results with moccasin venom in producing resolution of vesicles. Treatment by this method must be instituted early. Later than five days after the onset of the lesions, this method has shown little or no effect.

In addition to these one may mention as other therapeutic agents vitamin B, procaine injected into the skin, surgical Pituitrin, tetraethylammonium chloride administered intravenously, blood from the patient himself[10] or from a convalescent patient,[3] sodium iodide injected intravenously, filtered roentgen ray and placebo.

Dr. Boen Swinny of San Antonio suggested to the senior author in 1949 the use of inactivated influenza A and B virus vaccine in herpes simplex and zoster. Since that time we have treated more than 250 cases of herpetiform conditions with this vaccine. The procedure offers several advantages to the previously mentioned methods of treatment; aside from being at least as efficacious, it is easy to administer and lacks side reactions.

In this procedure we use a vaccine composed of equal parts of formalin-inactivated types A and B influenza virus prepared from the virus infected allantoic fluid of chick embryos. It is claimed that serum-neutralizing antibodies are produced in ten days following inoculation of this vaccine. Little or no immunity is produced in less than five days.[7]

Our method of treatment is to give .5 cc. subcutaneously as early as possible in the course of the disease and repeat the dose in twenty-four or forty-eight hours, and again, if necessary, within another forty-eight hours.

PRESENT SERIES

In a series of 100 cases of herpes zoster seen since 1949, there were 52 males and 48 females. Of the total, 63 patients were adjudged to have severe involvement, 30 moderately severe, and 7 mildly severe. Eighty-three patients had moderate to severe pain associated with the skin involvement.

Areas of involvement included the following: supra orbital 17, facial 10, neck 7, thoracic 25, lumbar 8, arm 5, leg 5, sacral 13, and scapular 17. Seven patients in this group showed involvement of two sectors (which explains the total of 107 areas).

Fifty-two per cent of the patients received three injections, and 5 severely affected ones received more than three injections. The average number of injections for the whole group was 2.64. Resolution of lesions manifested by drying of the vesicles and crust formation took place in 95 per cent of the cases within ten days or less. Ninety-two per cent showed good resolution in from five to seven days. Twenty-five per cent showed drying of the lesions within four days; 8 cases were resolved in twelve to fourteen days. All cases showed resolution of lesions within fourteen

days with the exception of 5 patients who had secondary infection. The average duration of vesiculation before resolution began was 5.56 days.

Forty-two patients experienced improvement of pain in forty-eight hours or less following the initial injection.

Postherpetic pain of one month or longer was found in 5 cases. One patient had postherpetic pain for three weeks, 4 for fourteen days, and 2 for seven days following the initial injection. It is our opinion that the vaccine was of no effect in combating persistent pain.

There was no question but that the outlook for satisfactory results was materially enhanced by the early administration of the vaccine. Patients who had the dermatologic lesions for a week or longer and had neuralgic pain showed considerably less response to therapy than patients with disease of shorter duration, as well as a greater probability of postherpetic neuralgia. Generally speaking, a person with herpes zoster who was 45 years or older usually had pain with the initial herpetiform lesions and was considerably more inclined to have a postherpetiform neuralgia than younger patients. There have been no cases of ulceration of the cornea encountered since we instituted this form of therapy.

Occasionally mild headache and malaise were encountered, but this disappeared within twenty-four hours. Local redness and tenderness at the site of the injection was negligible and deemed of no importance.

Calamine lotion, N. F. or isopropyl alcohol and occasionally antibiotics as well as superficial roentgen ray were used locally for secondary infections.

HERPES SIMPLEX

Approximately 150 patients with herpes simplex who received similar injections of influenza virus vaccine showed 67 per cent response to one injection of the vaccine. It is our opinion that more prompt resolution of the lesions than usual resulted from this mode of therapy.

Some patients who had recurrent episodes of herpes simplex were convinced that a series of five injections given at weekly intervals materially prevented the recurrent outbreaks for a period of seven to nine months. Permanent immunity apparently is not produced by this treatment.

SUMMARY AND CONCLUSIONS

A series of 100 cases of herpes zoster seen in private practice is reviewed. These patients received one or more .5 cc. injections of type A and B influenza virus vaccine. The average number of days after treatment was first given before resolution of the vesicles occurred was 5.56; there was an incidence of 5 per cent postherpetic pain of one month or longer. The number of days between treatment and resolution of the lesions corresponded satisfactorily with other approved methods of treatment. The number of days between treatment and resolution in control patients in the series was in accord with another study of patients treated with only an analgesic in which ten days intervened on the average.[6]

Influenza virus vaccine undoubtedly is of value in the treatment of herpes zoster by inhibiting the appearance of new lesions, drying up old lesions, lessening pain in early cases, and contributing to a low incidence of postherpetic complications, although it appears to be of no effect on postherpetic pain. Moreover, the ease of administration, lack of side reactions, and low cost of the treatment make it satisfactory for the ambulatory office patient.

Herpes simplex also responds promptly to injections of influenza virus vaccine.

REFERENCES

1. Andrewes, C. H.: Tissue-Culture in Study of Immunity to Herpes, J. Path. & Bact. *33*:301-312 (April) 1930.

2. Bailey, P.: Herpes Zoster, Postgrad. Med *12*:127-132 (Aug.) 1952.

3. Becker, F. T.: Herpes Zoster Ophthalmicus; Results of Treatment with Transfusions of Convalescent Blood, Arch. Dermat. & Syph. *58*:265-275 (Sept.) 1948.

4. Bondurant, C. P.: Attenuated Virus in Autogenous Blood Serum as Therapeutic Agent in Herpes Zoster, South. M. J. *45*:529-533 (June) 1952.

5. Dennie, C. C.; Morgan, D. B.; and Coombs, F. P.: Treatment of Herpes Zoster with Moccasin Venom, J. Invest. Dermat. *12*:153-155 (March) 1949.

6. Ebert, M. H.: Histologic Changes in Sensory Nerves of Skin in Herpes Zoster, Arch. Dermat. & Syph. *60*:641-648 (Nov., pt. 1) 1949.

7. Hale, W. M.: and McKee, A. P.: Value of Influenza Vaccination When Done at Beginning of Epidemic, Am. J. Hyg. *42*:21-27 (July) 1945.

8. Kass, E. H.; Aycock, R. R.; and Finland, M.: Clinical Evaluation of Aureomycin and Cloramphenicol in Herpes Zoster, New England J. Med. *246*:167-172 (Jan. 31) 1952.

9. Ormsby, O. S.: Practical Treatise on Diseases of Skin for Use of Students and Practitioners, ed. 5, Philadelphia, Lea and Febiger, 1937.

10. Poth. D. O.: Autohemotherapy of Herpes Zoster; Results in 154 Cases, Arch. Dermat. & Syph. *60*:636-638 (Oct.) 1949.

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For every dollar a medical school accepts in research grants, it has to use an average of 35 to 40 cents of its own funds to meet indirect costs arising from the grants, according to a recent study quoted in the June, 1953, *Medical Advance*, published by the National Fund for Medical Education.

The younger a physician is, the more prescriptions he writes, *Medical Economics* has determined. Results of a questionnaire sent to 134,000 physicians indicate that doctors with less than ten years' experience tend to write about 70 per cent more prescriptions annually than their colleagues with thirty or more years of experience, although both treat about the same number of patients. The average doctor in 1951 wrote 2,517 prescriptions—1 for every 3 patients examined.

OFFICE MYCOLOGY
Report on 1,000 Cultures Taken in a General Dermatologic Practice

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IN the past three years, I have recorded carefully certain data on every culture taken in my office for mycologic reasons. One thousand consecutively taken cultures are herewith analyzed, with these questions in mind:

1. What pathogens, and in what numbers, are routinely encountered in this part of the country?
2. How many and what kinds of contaminants abound?
3. There are certain situations in which the general medical profession usually takes it for granted that all involvements are apt to be fungous in nature. This is especially pertinent in regard to feet, all of the ills of which are apt to be named "athlete's foot"; otitis externa, which most of our colleagues who are not dermatologists associate with swimming pools and/or fungi; and certain resistant examples of eczema of the hands. How often are fungi actually found in these circumstances?
4. How often are dermatoses of other regions found to be of fungous origin?
5. What is the relative value of direct examination of infected material on slides as compared with examination by means of culture?

PATHOGENS ENCOUNTERED

In table 1 will be seen a composite of all pathogenic forms met in this series. Features of interest in this table include the following:

Totals marked with asterisks: These six fungi are singled out only to draw attention to the number of different areas of the body subject to attack by these respective species. Perhaps we physicians do not always bear in mind the potential ubiquitousness of several ordinary pathogens.

Scalp ringworm: In this series there is a considerably larger proportion of canis to audouini than is generally being reported in the literature. I do not know the reason for this. Incidentally, in the three months since these figures were compiled, I have seen 7 new cases of scalp attacked by Trichophyton tonsurans as against only 4 in the previous three years. Valuable observations and data regarding this type of scalp infection are to be found in the recent excellent paper by Pipkin.[15]

Read before the Texas Dermatological Society, Houston, April 26, 1953.

Fungi of dubious pathogenicity: I have purposely included 3 organisms in this table (Aspergillus, Candida parakrusei, and Allescheria) the etiologic role of which as dermal pathogens is in question. In each case, the organism (and, as far as could be determined, the same species thereof) was isolated at least twice, usually oftener, from the indicated sites. Therefore, either the organisms were carried consistently in these areas as saprophytes or (barely possible) were pathogenic in some cases. (It should be borne in mind that all cultures in this series were taken from areas showing dermatoses or onychiae, and not from normal appearing regions.)

CONTAMINANTS

The contaminants found in this study are shown in table 2. Those marked with asterisks were thought to be possibly pathogenetic.

(A few words must be inserted here to explain the disproportionately large number of contaminants for this size series. The excessive number is largely due to an invasion which descended upon my laboratory during the third year of this study, consisting of tiny laboratory mites which resemble the Acarus scabiei. These vicious little pests travel from bottle to bottle, thoroughly mixing up all cultures. After battling them for sixty days, I was finally forced to throw out my entire collection of cultures, call in the exterminators, and start all over again.)

In dealing with contaminants, the observer should always remember that nonpathogens can emulate cultural characteristics of fungi known to be pathogenic. On the other hand, important pathogens may look deceptively like contaminants; an example is an organism like Sporotrichum schencki, the jet-black colony of which always suggests contamination. Therefore it is well worth while to attempt identification of all contaminants.

SITES OF FUNGI

Next should be considered the incidence of fungi in various areas of the body. First I wish to present my figures on the incidence of fungi in dermatoses of feet, hands, and ears. These areas are selected for reasons mentioned in the third numbered paragraph of the introduction.

Feet.—In table 3 the findings on foot cases are

summarized. It should be remembered that in all cases a dermatosis existed; in other words, almost no studies on routine cases of dermatophytosis and none on healthy looking feet are included.

The large number of negative findings speaks for itself: 60 per cent in all, and this in the practice of a dermatologist whose clinical judgment was that most of these might be mycotic.

It is not the purpose of this presentation to discuss differential diagnosis of foot dermatoses, but I should like to remark on shoe leather dermatitis.[8, 21] their absence, just as was the case with the shoe leather dermatitides.

Ears.—In the past six or eight years, a great deal of attention has been manifest in the literature on the flora associated with otitis externa. It is universally found in all thoroughgoing studies that fungi are always distinctly in the minority and that bacteria predominate; and most workers ascribe a very important role to Pseudomonas aeruginosa.[4, 10, 17, 18]

In this study, similar conclusions were reached. Of the fungi found (table 1) Candida albicans predominated. However, overall figures show thus: no growth 54 per cent, fungi 19 per cent, and bacteria 27

TABLE 1.—*Summary of Pathogenic Fungi Found.*

	Scalp	Ears	Face & Neck	Oral Cavity	Upper Extremities	Hands & Fingers	Axillae	Rest of Torso	Male Genitalia	Female Genitalia	Male Pudendum	Female Pudendum	Buttocks	Lower Extremities	Feet Dorsa	Feet Plantae	Feet Digital	Nails, Fingers	Nails, Toes	Totals
M. audouini	19				1			1												21
M. canis (lanosum)	62	2	8		8	1	1	5						5		1				93*
M. gypseum (fulvum)	4						1													5
T. tonsurans	4																			4
T. rubrum (purpureum)		1				2	1	3			4	2	15	2	1	1	4		1	37*
T. mentagrophytes	1				1			1	1				1	2	1	10	3			21*
T. violaceum	10												1							11
C. albicans	5	14		7	2	7	1	2		15	12	3	1	1	3	2	4	15	4	98*
C. krusei					1	1	1				2	2				1	2	1	1	12*
Sporotr. schencki						2														2
Blastom. dermatitidis											2									2
E. floccosum (inguinale)											3			1			1			5
Crypt. neoformans																		1		1
Aspergillus sp.	3	4	4		1	2		2	1	2	4	1		1	2	2	8	3	11	51*
T. rosaceum																1				1
C. parakrusei		1																		1
Allescheria sp.																			1	1

*Fungi appearing in 9 or more different areas of the body.

A large number of the mycologically negative cases proved to be due to sensitization to foot gear; and it was indeed a striking observation as to how infrequently there was any concomitant fungus present.

It behooves dermatologists to drive home to their colleagues the points that the foot is subject to a good many other dermatoses; that fungous disease even if present may be irrelevant or merely predisposing to other pathologic conditions; and that therefore laboratory evidence, if negative, almost certainly rules out mycosis, while if positive, does not necessarily establish a primary causal relationship.

Hands.—In appraising hand cases mycologically (table 3) we find the probabilities of demonstrating fungi to be much lower than on the feet. Only 22 per cent of cases considered possibly mycotic were able to produce positive findings—which would be an incidence of perhaps 3 to 5 per cent of all hand dermatoses seen. Again I wish to point out that in most cases in which definite or probable etiology could be established, fungi were conspicuous by per cent; of the bacteria 11 per cent were Pseudomonas and 8 per cent Staphylococci.

It should be borne in mind that this work was carried out almost entirely with mycologic media, not especially conducive to bacterial growth. Undoubtedly a large number of the negative 54 per cent would have grown bacteria in suitable media.

Nails.—Percentagewise, the nails were the most fruitful field in this study next to the scalp, showing 55 per cent positive results (table 4). Inciden-

TABLE 2.—*Contaminants Found.*

Allescheria sp.	2*	Hormodendrum sp.	8
Alternaria sp.	2	Macrosporium sp.	1
Aspergillus		Monilia sitophila	3
glaucus	6	Mucor sp.	1*
fumigatus	8*	Mycelia sterila	3
niger	20	Penicillium sp.	4
flavus	3*	Phoma sp.	1
terreus	2*	Pullularia pullulans	2
unidentified sp.	61	Rhinotrichum sp.	3
Botryotrichum	1	Rhizopus sp.	1
Chaetomium sp.	2	Scopulariopsis sp.	1
Cryptococcus sp.	15	Streptomyces sp.	1
Fusarium sp.	2	Trichosporon sp.	1
Helminthosporium sp.	5	Unidentified	231

*Possibly pathogenetic.

tally, I was repeatedly impressed by a fact noted by Williams and Barthel[20] some time back, namely, that fungi can be recovered from nails showing surprisingly few abnormalities.

In spite of the relatively high returns of positive findings, nails, too, are somewhat overrated mycologically in the minds of most of the medical profession. Here again dermatologists should expend effort to teach that all is not fungous that is yellow, opaque, or distorted. If fungus is assumed to be present, it ought to be demonstrable in the laboratory—especially if more than one attempt is made.

TABLE 3.—*Comparison of Results of Slide Examination and Cultures Together with Flora Found on Hands and Feet.*

Hands		Feet	
Slide +, Culture +	2	Slide +, Culture +	14
T. rubrum	1	T. rubrum	1
Aspergillus	1	Aspergillus	4
		C. albicans	2
		M. canis	1
		E. floccosum	1
		T. mentagro.	5
Slide 0, Culture +	14	Slide 0, Culture +	34
T. rubrum	1	T. rubrum	6
Aspergillus	2	Aspergillus	10
C. albicans	7	C. albicans	6
C. krusei	1	C. krusei	2
T. mentagroph	1	T. mentagroph	8
Sporotr. schencki	2	T. rosaceum	1
		C. parakrusei	1
Slide +, Culture 0	7	Slide +, Culture 0	28
Slide 0, Culture 0	80	Slide 0, Culture 0	117

General Skin Surfaces.—The figures from the general skin surfaces (excluding such areas as hands, feet, nails, scalp, and mucosal-skin junctures) are assembled for convenience in table 5.

By and large, this group represents the less baffling diagnostic problems. Response to therapy is favorable, as a rule, with the notorious exception of infections of Trichophyton rubrum (purpureum) the refractoriness of which to treatment is well known to all dermatologists.

SLIDES VERSUS CULTURES

The preparation of an extemporaneous slide for direct examination is a procedure available to almost any physician. Culture study is commonly done now by most dermatologists and most clinical laboratories. There have been published many studies of the percentage results obtained by each method in many various groups: series of sailors,[1] college students,[14] soldiers,[11] dermatophytosis cases,[19] scalp cases,[6] and others. Figures from this study are reported here on a similar basis; however, no group quite comparable to this one was encountered in the literature.

Table 6 summarizes results in the four areas commonly investigated by dermatologists, other than the scalp. The latter is left out of this discussion because (1) the chief information about it was shown in table 1 and (2) in skilled hands, positive identification of organisms causing tinea capitis runs from 86 to 97 per cent accurate.

In looking at this table one bears in mind that all these tests were prepared from areas which were sick, not healthy, and in almost all cases, there was a tolerable possibility of the presence of fungous disease as suggested by clinical judgment.

One set of interpretations we can draw is this: If one examines mycologically many pairs of feet on which there is clinical suspicion of fungous disease, he will find positive evidence of one sort or the other in 40 per cent, none in 60 per cent. On hands, however, only about half as many (22 per cent) will be positive. In the cases of nails, 55 per cent will prove positive; 45 per cent negative. Body lesions will yield a similar number of positives, 55 per cent.

TABLE 4.—*Comparison of Results of Slide Examinations and Cultures Together with Flora Found on Nails.*

Fingernails		Toenails	
Slide +, Culture +	3	Slide +, Culture +	2
C. albicans	3	C. albicans	1
		Aspergillus	1
Slide 0, Culture +	17	Slide 0, Culture +	18
C. albicans	13	C. albicans	4
C. krusei	1	C. krusei	1
Aspergillus sp.	2	Aspergillus sp.	10
Crypto. neoform.	1	T. rubrum	1
		Allescheria sp.	1
		Mucor sp.	1
Slide +, Culture 0	5	Slide +, Culture 0	7
Slide 0, Culture 0	22	Slide 0, Culture 0	22

Slides Positive, Cultures Negative.—In this connection, it is appropriate to speculate on the reasons for discrepant results between slides examined directly and cultures, especially in the case of positive slides and negative cultures. From a theoretical standpoint, this should seldom occur. Obviously, if organisms flourish to the extent that they can be found in a small sampling placed on a glass slide, they should certainly be demonstrated by culture. How can the many instances where this fails to happen be explained?

The reasons ordinarily thought of are as follows: (1) the material planted may not have contained fungi—even though the adjacent, slide-examined area

did; (2) recent use of fungicides may have suppressed viability; (3) pathogens may have been overgrown by saprophytic contaminants; and (4) fungus may have been present and viable, but refused to grow, or required special enrichment or adjuvants.[2, 9, 12, 13]

Slides Negative, Cultures Positive.—Now as to the converse condition: Why would the slides often fail to demonstrate fungi later proved by cultures to exist?

TABLE 5.—*Comparison of Results of Slide Examinations Together with Flora Found in Glabrous Lesions.*

Slide +, Culture +			52
T. rubrum	12	M. canis	17
T. mentagroph	3	M. audouini	2
T. violaceum	1	M. gypseum	1
C. albicans	7	Aspergillus sp.	8
C. krusei	1		
Slide 0, Culture +			72
T. rubrum	17	M. canis	10
T. mentagroph	2	M. audouini	3
T. violaceum	1	Aspergillus sp.	8
C. albicans	20	C. parakrusei	1
C. krusei	8	Blastom. dermat.	2
Slide +, Culture 0			52
Slide 0, Culture 0			146

(1) Here apparently faulty technique can much more often be the likely cause: debris must be cleared away, both exudates and medicaments, and often the scalpel has to scrape deeply to demonstrate fungi. (2) In this group fungicides are much greater interferers. (3) One other factor is diligence in examining the slide. I save practically every negative slide at least overnight and give it one more good look before discarding. A slide many times is positive the next day when it was negative within the first few hours.

In this study, the only further light I can shed is that far and away the largest number of species I find on cultures where the slide was negative are Candidae; second and third places are held by the two common Microspora though the number is a great deal less than the Candidae.

TABLE 6.—*Summary of Results from Slide Examinations and Cultures.*

Region	No.	Positive: Had Slide Only Been Done	Positive: Had Culture Only Been Done	Positive: When Both Were Done	Negative	Per Cent: +	Per Cent: 0
Feet	193	42	48	76	117	39.4	60.6
Hands	103	9	16	23	80	22.3	77.7
Nails	96	17	40	52	44	54.2	45.8
Glabrous	320	104	122	174	146	54.4	45.6
					Average	45.7	54.3

COMMENTS

In 1940 Downing and his group[6] at Massachusetts General Hospital stated, "In 476 patients in whom existence of fungous disease was definitely or remotely suspected, 37.6 per cent gave positive findings." In my series of 812 different patients, the figure is 41.3 per cent. This is a fairly close correspondence.

But apart from figures and statistics, certain general impressions have been gained. For one thing, I am rather definitely of the opinion that fungi as secondary invaders occur relatively seldom—in the manner, that is, that bacteria so frequently invade loci minoris resistentiae. I think a good illustration of this fact is the comparative infrequency of ringworm in dermatitic hands; certainly this organ has a maximum of opportunity for acquiring this disease if it is to be acquired as a secondary infection. In determining whether an area will or will not become fungus infected, the major roles are played by factors other than simply the integrity of the epidermis; and on this basis, for instance, maceration of the feet is more likely an effect than a cause of dermatophytosis. Often enough I have been unable to demonstrate fungi in sadly macerated feet.

What these other factors are of course is not known entirely. Probably they are mostly local biochemical and physicochemical conditions; witness the promising studies of the antifungal qualities of adult hair fat by Rothman and his group[16] in elucidating a probable explanation for the immunity of the postpuberal scalp to tinea capitis.

In this connection, despite the disappointing results from injections of fungous extracts, I believe that the vast amount of work done two decades ago along immunologic lines strongly suggests that systemic factors are of major import.

Finally, I should like to join the ranks of those who believe that the demonstration of a known pathogenic fungus by culture practically invariably betokens clinical infection.[3, 5] I am well aware of reports[7] showing pathogens on ostensibly normal skin in amounts ranging from 1 to 5 per cent. It is not too difficult to hypothecate explanations for these findings. One is, these normal groups are almost always transient subjects—college students at entrance examinations, for instance—and not patients with charts and histories. Who knows how many of these persons with positive tests broke out with ringworm the next day or the week after the survey? Another explanation is that fungi can lie dormant for long periods, and at such times the skin is clinically normal. Furthermore, one host can have the local immunologic factors to suppress a live fungus from flourishing on him; he is therefore a carrier in the bacteriologic sense, and his positive culture is of clinical significance.

SUMMARY

Diligent examination of skin cases for fungi is a rewarding procedure. Frequently, diagnoses are confirmed and established; occasionally, unlikely-seeming cases prove to be mycotic in origin. On the other hand, and equally important, quite often the presence of fungi can be ruled out in conditions wrongly assumed to be mycotic.

The kinds and relative frequency of skin pathogens encountered in 1,000 consecutive cultures are reported. The numbers, kinds, and percentage of fungi found in tinea of hands, feet, nails, scalp, ears, and glabrous lesions are detailed. Types of contaminants which infested this study are reported.

The relative diagnostic values of slide versus culture methods in various circumstances and regions are examined, and some reasons for discrepant results are discussed.

Some impressions gained relative to pathogenicity and invasiveness of fungi are presented.

REFERENCES

1. Ajello, L.; Keeney, E. L.; and Broyles, E. N.: Observations on Incidence of Tinea Pedis in Group of Men Entering Military Life, Bull. Johns Hopkins Hosp. *77:*440-447 (Dec.) 1945.
2. Benham, R. W.: Effect of Nutrition on Morphology and Growth of Dermatophytes; Development of Macroconidia in Trichophyton Rubrum, Mycologia *40:*232-240 (March-April) 1948.
3. Burgess, J. F.: Fungus Infections of Skin; Cultural Study of Flora of Ringworm, Arch. Dermat. & Syph. *12:*853-857 (Dec.) 1925.
4. Conley, J. J.: Evaluation of Fungous Disease of External Auditory Canal, Arch. Otolaryng. *47:*721-745 (June) 1948.
5. Cornbleet, T.: Cultures from Skin of Apparently Normal Feet, Arch. Dermat. & Syph. *13:*670-671 (May) 1926.
6. Downing, J. G.; Merrill, B.; and Belding, D. L.: Clinical and Laboratory Study of Incidence of Fungi in Patients with Cutaneous Eruptions, New England J. Med. *222:*263-266 (Feb. 15) 1940.
7. Downing, J. G.; Nye, R. N.; and Cousins, S. M.: Investigation of Fungous Flora of Apparently Normal Skins, Arch. Dermat. & Syph. *35:*1087-1092 (June) 1937.
8. Gaul, L. E., and Underwood, G. B.: Primary Irritants and Sensitizers Used in Fabrication of Footwear, Arch. Dermat. & Syph. *60:*649-675 (Nov., Part 1) 1949.
9. Georg, L. K.: Influence of Nutrition on Growth and Morphology of Dermatophytes, Tr. New York Acad. Sc. *11:*281-286 (June) 1949.
10. Gill, W. D., and Gill, E. K.: Otitis Externa; Some Comments Concerning Present Status of Therapy, South M. J. *43:*428-431 (May) 1950.
11. Hopkins, J. G., and others: Dermatophytosis at Infantry Post; Incidence and Characteristics of Infections by 3 Species of Fungi, J. Invest. Dermat. *8:*291-316 (June) 1947.
12. Littman, M. L.: Culture Medium for Primary Isolation of Fungi, Science *106:*109-111 (Aug. 1) 1947.
13. Mandel, E. H.; Muskablit, E.; Franks, A. G.; and Herrmann, F.: New Clearing Method Permitting Same Specimen to Be Examined Microscopically for Pathogenic Fungi and Directly Inoculated into Culture Media, J. Invest. Dermat. *18:*61-70 (Jan.) 1952.
14. Maples, M. J., and di Menna, M. E.: Survey of Incidence of Interdigital Fungous Infection in Group of Students from University of Otago, M. J. Australia *2:*156-161 (July 30) 1949.
15. Pipkin, J. L.: Tinea Capitis in Adult and Adolescent, A.M.A. Arch. Dermat. & Syph. *66:*9-40 (July) 1952.
16. Rothman, S.; Smiljanic, A.; Shapiro, A. L.; and Weitkamp, A. W.: Spontaneous Cure of Tinea Capitis in Puberty, J. Invest. Dermat. *8:*81-98 (Feb.) 1947.
17. Senturia, B. H.: Etiology of External Otitis, Laryngoscope *55:* 277-293 (June) 1945.
18. Senturia, B. H.: Diffuse External Otitis: Its Pathology and Treatment, Tr. Am. Acad. Ophth. *55:*147-159 (Nov.-Dec.) 1950.
19. Weidman, F. D.; Emmons, C. W.; Hopkins, J. G.; and Lewis, G. M.: War and Dermatophytosis, with Special Reference to Treatment and Fungicide Testing, J.A.M.A. *128:*805-811 (July 14) 1945.
20. Williams, C. M., and Barthel, E. A.: Tinea of Toe-Nails as Source of Reinfection in Tinea of Feet, J.A.M.A. *93:*907-910 (Sept. 21) 1929.
21. Winkler, M. A.: Common Conditions of Feet Often Confused with Fungus Infection, Rhode Island M. J. *34:*585-587; 590 (Nov.) 1951.

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GENERAL ASPECTS OF STRABISMUS

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THE purpose of this paper is twofold: (1) to review some of the general problems encountered in treating patients, particularly infants and children, who have strabismus, and (2) to present ideas for managing these problems so that physicians other than ophthalmologists may know better what to tell the parents and when to make appropriate referrals.

Actually, the title as given is almost a misnomer. Deviation of the eyes now is seldom called strabismus. The term heterotropia is used to designate any deviation of the eyes. Usually when this term is used, physicians think of the child with a large deviation that is obvious on casual observation. Actually, deviation is a matter of degree, and there is another large group in which there is a strong imbalance of the muscles, or tendency to deviate, but in which the eyes are held straight by fusion. This tendency to deviate is called heterophoria. There are some who fall between these two groups in that their eyes deviate only part of the time. In most instances they have marked muscle imbalance, or heterophoria, but enough fusion to hold the eyes straight most of the time. However, when the child is sick, tired, or nervous, the eyes will deviate. This is called an intermittent heterotropia. Prefixes are used to designate the direction of the deviation so that any condition may be denoted by its name. Esotropia designates turning in; esophoria, a tendency to turn in; exotropia, turning out; and exophoria, a tendency to turn out. Similarly the prefix *hyper-* designates turning up (with the other eye turning down) and *cyclo-*, a torsional deviation.[2] Frequently patients who have a tropia, but good vision in each eye, may freely alternate fixation with either eye while the

other one deviates. They are designated as having an alternating esotropia or exotropia, as the case may be. If only one eye deviates, the terms right esotropia or left esotropia are used. For example, a child with right esotropia would have a right eye turning in toward the nose while the left eye fixates. Frequently these patients have diminished visual acuity in the deviating eye.

ANATOMY AND PHYSIOLOGY

Each eye has six oculorotary muscles. The medial and lateral recti are the lateral rotators and have only one action each, their effective working angle with the globe being 90 degrees. There are four vertically acting muscles: the superior and inferior recti, and the superior and inferior obliques. The vertical recti meet the globe at an angle of about 25 degrees from the visual axis in the primary position, and the obliques at about 54 degrees. Thus, none of the vertical muscles work from an angle of 90 degrees, and each has not one, but three actions. The amount of each of these actions varies according to the position of the eye. For example, the superior rectus not only elevates the globe but also acts as a medial rotator and intorter. It is easy to understand that a horizontal deviation is much simpler to deal with than a vertical deviation; and when both horizontal and vertical deviations are present, the problem may become more complex.

With these facts in mind, let us briefly review a child's visual acuity, accommodation, and fusion development.

Visual acuity itself is of relatively low order at birth and does not reach the 20/20 level until a child is 5 or 6 years of age. There is some disagreement about the early refractive error, but by the age of 1 year the normal eye is about 2 diopters hyperopic. This gradually decreases until adult growth is completed. Accommodation itself is not strong before the age of 2 years, probably being fully developed at age 3 to 4 years. Fusion is the superimposition of the image presented by each eye so that single binocular vision results. In each eye there are corresponding retinal points to receive the light stimulus from any given point of the object being observed. This stimulus of each eye is then fused into one image so that single binocular vision results. This is the means by which stereopsis or most depth perception is obtained. It is also this fusion faculty which overcomes small phorias to hold the eyes straight, and it is responsible for keeping the eyes straight after surgery. The development of fusion is difficult to evaluate, but normally is probably steadily developed until the age of 6 or 7 years.[5] If the eyes are deviated so that there is no chance for fusion to develop until after the child is 6 years of age, it can be developed in only a small percentage of cases. Thus, it is of the utmost importance that the eyes be placed in mechanical alignment at an early age so that there is an opportunity for normal fusion to develop.

There are three possible things that can happen to the visual physiology when the eyes cross: (1) the child sees double, or (2) he suppresses the image of one eye to prevent seeing double, or (3) abnormal retinal correspondence develops. It is easy to demonstrate diplopia by pulling on one's lids enough to pull the eye out of line. Seeing double is confusing and in children is not tolerated long before suppression develops. In the case of the monocular deviator, only the deviating eye is suppressed and vision may be reduced in this eye to about 20/200 or less. If the child alternates the eyes, the visual acuity remains good in both, but the brain suppresses the image of whichever one is deviating at the time. Abnormal retinal correspondence is a developed pattern wherein the retinal points in each eye that normally correspond are replaced functionally by other points, and the child actually has single binocular vision while one eye deviates. In such cases the visual acuity is not normal because the retina is not constructed so that 20/20 vision is possible anywhere except at the macula. Nonetheless, nature tries to overcome the defect. The presence of abnormal retinal correspondence makes a cure more difficult, for after the eyes are straightened, the habit again must be changed so that the normal anatomic corresponding points of each eye correspond functionally.

ETIOLOGY

The etiology of heterotropia has long been discussed and many classifications have been presented. It will only be mentioned here that three broad categories can be made: sensory, motor, and central. Sensory obstacles may be anything interfering with proper retinal imagery of either eye, such as poor illumination, refractive error, opacities of the media, and retinal and optic nerve lesions. Motor obstacles are mechanical defects located in the motor apparatus of vision and may lie in the lids, orbits, globe, or muscles themselves. Scobee recently stated that he believed 90 per cent of lateral deviations were due in part to some mechanical element.[6] Central obstacles include hypertonicity of the convergence center, lesions of the nuclei, and psychogenic influences. One of the chief causes of early cases of heterotropia is thought to be birth trauma. In one series studied, retinal hemorrhages were visible in 40 per cent of babies of normal birth, with a higher percentage in cases in which delivery was complicated by a required high forceps intervention.[5] It is assumed from this that there are also minute hemorrhages in the brain and muscles. Those occurring around the nerves or nerve nuclei may account for many cases of heterotropia. Heredity plays a big

part in heterotropia. Post recently stated the belief this is one of the main factors.[4]

The following six facts are important to know about any case:

1. What was the time of onset? A tropia present from birth is likely to be due to a birth injury or some anatomic anomaly. This is not to be confused with the normal eye deviations found in all babies which disappear by the age of 6 months to 1 year. I am speaking of a large and constant deviation that is obvious even on casual observation. Those tropias that begin when the child is about 2 to 3 years frequently have a large accommodative component, with the child showing more than the normal amount of hypermetropia. In those children in which the deviation does not begin until 5 or 6 years of age, a large functional element usually is present. This sometimes occurs when the child begins school and meets new problems. Of course this is only a rough grouping. Most physicians have seen tropias begin at any given age. A childhood illness may convert an existing phoria into a tropia, either by affecting the oculorotary system directly or by systemic weakening. At one time measles was stated to be the chief cause of crossed eyes.[1]

2. Is the deviation constant or intermittent? Constant deviations are of more concern and demand more immediate attention. Frequently in the case of intermittent deviations there is some fusion present. Constant deviations of large degree should have surgery early if not helped by glasses.

3. Is the amount of deviation fixed or variable? Those patients showing variability may have a large innervational component and should be treated conservatively. If and when surgery is done, it usually should be done with the smallest amount of deviation in mind. These statements regard esotropia only and do not apply to exotropia.

4. Is the deviation monocular or alternating? By this is meant does the child habitually fix with one eye while the other deviates, or does he freely alternate fixation with either eye. In the first instance the vision in the deviating eye either is poor to start with, becomes so secondarily, or is a combination of both.

Brief mention should be made of amblyopia exanopsia. In the monocular squinter there may be some deformity in the nerve or retina, or refractive error of the squinting eye, the fixing eye being relatively normal. In the case of unequal refractive error, glasses alone may give a full correction. On the other hand, one eye may deviate solely because of a paretic muscle or other trouble in the neuromuscular system. In this event the vision in the deviating eye will be poor because of suppression. This is considered by Scobee to be a conditioned reflex called suppression amblyopia.[5] A term of longer standing is amblyopia exanopsia. In such cases normal vision may be reestablished by occlusion of the sound eye to force fixation with the deviating one. This will be discussed in more detail later.

5. Is there a vertical element present? In small children it is difficult but important to check for minute amounts of vertical displacement The normal adult with well developed fusion can overcome only 3 prism diopters of vertical displacement and maintain single binocular vision. This is in distinction to about 25 prism diopters of horizontal displacement that most persons can overcome. Thus, any vertical imbalance can be a serious obstacle to fusion and may convert an existing lateral phoria into a tropia. Correcting a small amount of vertical displacement may enable the child himself to correct a much larger horizontal displacement.

6. Is the deviation concomitant or paretic? The term concomitant is used to describe those deviations which do not vary significantly in the six cardinal directions of gaze. This is most common in children having lateral deviations. Paretic deviations are most marked in the field of action of the involved muscle and are present in about 98 per cent of vertical deviations.[7]

TREATMENT

Treatment in general can be divided into three main categories: glasses, exercises, and surgery.

Glasses are given for two reasons: either to correct refractive error or to correct minor vertical deviations by means of prisms, or both. Glasses may encourage fusion by clearing the patient's vision, or in the case of the hyperope, by abolishing the need for excess accommodation and thus reducing the convergence stimulus. In the case of moderate degrees of deviation and relatively large refractive errors, glasses alone are sufficient frequently to hold the eyes straight. As the child grows older and fusion develops, the amount of plus in the glasses gradually can be reduced, and it is desirable to do so. In other cases glasses may partially reduce the deviation, and in still others may make no difference whatsoever. Opthalmologists often prescribe glasses for children as early as 18 months of age when a large refractive error is observed. If the error is large enough that the glasses improve the child's vision appreciably, there is no difficulty in getting the child to accept them. If on the other hand, the child has only a moderate degree of hyperopia and can see as well without his glasses, it sometimes is difficult to persuade him to wear them.

If glasses alone do not do the job, exercises are to be considered. In larger cities where orthoptic technicians are available, training can be given in developing fusion. There is no doubt in my mind that the overall percentage of functional cures can be in-

creased by such training when it is indicated. However, it is frequently a lengthy process, and in the South there are few certified technicians. Even without an orthoptist, some exercises can be carried out at home to help break up suppression and abnormal retinal correspondence, as well as to train convergence.

In the monocular deviator the image of the deviating eye is frequently suppressed and poor vision in this eye results. Vision can be improved by forcing the child to use his bad eye by covering the good one. This is a conditioned reflex, and in order to be broken up with any dispatch, the occlusion must be constant. The method that I have found most satisfactory is the application of an Elastoplast Eye Occluder made by Duke Laboratories. This is a flesh-colored adhesive shaped to fit the eye. It has a gauze center so that the lids and lashes will not become stuck to the tape. When it is in place, there is no way for the child to peep out of its sides. Glasses may be worn over it for the benefit of the other eye. A black occluder worn on the glasses is worse in cosmetic appearance and the child frequently manages to look around it. One can imagine the distaste a child has for covering up his good eye in which he probably has 20/20 vision and having to use an eye that probably has only 20/400. This sometimes requires a lot of selling to the child, his parents, and his schoolteacher. Occlusion is so important in the treatment that when a child has been neglected until after he has started school. I do not hesitate to recommend it during the school year, even at the expense of the child's losing a semester. Seldom is this necessary, for after a few weeks of constant occlusion, the vision usually reaches a useful level.

A trial of four weeks is sufficient in young children to determine whether or not the vision can be improved. If there is no improvement either near or at at distance, further occlusion is probably useless. If the vision has improved, the treatment should be continued until maximum improvement is attained. This is usually accomplished within two or three months. After vision has improved to 20/40 or better, an occluder lens or lacquered lens may be substituted for the adhesive. When maximum vision is reached and if the case requires surgery, it should not be delayed. To do so invites development of abnormal retinal correspondence. The older the patient, the longer the time required to break up the suppression amblyopia. It is usually practical to treat those aged 12 years or less. Cases have been reported in which adults reached 20/20 vision in the amblyopic eye after an accident cost them the sight of the good eye. Considerable time is required in treating such cases. Post had a patient who lost his good eye when in his late fifties and after three years reached normal visual acuity in the other.[3]

For a great many patients surgery is necessary, either early or after glasses and orthoptics have been tried. Usually if a patient's residual deviation is more than 18 prism diopters (9 arc degrees), surgery is indicated. As mentioned earlier, the constancy of the deviation is of the utmost importance in considering surgery, and surgery should always be done for the least amount of deviation present. If a child has a large and constant deviation from birth, surgery should be done early—at about 18 months of age. The first operation may not be sufficient and more surgery may be needed later, but the eyes should be put in a position early to allow normal development. Parents should always be told that more than one operation frequently is necessary. There are too many factors involved for the amount of surgery done to bear a constant relationship to the degree of correction obtained. For example, it is not unusual for a muscle to seem quite paretic. For the sake of illustration, let us say that the right lateral rectus is paretic and will not move the right eye externally beyond the midline. After a recession of its antagonist, the right medial rectus, the lateral rectus may regain tone and act more normally, thus giving more correction from the surgical result. Another possibility is that at the time of recession of the right medial rectus, the muscle may be found to have some abnormal attachments holding it down and preventing it from relaxing and allowing the eye to turn out. Cutting of these anomalies, as well as recession of the muscles, will sometimes give a marked amount of correction. Many cases have both a vertical and horizontal component, and it is seldom wise to try to correct both of these conditions in one operation.

Physicians would like to shoot for the moon and aim at fusion in all cases. This is by no means possible to attain. In the light of present knowledge it is not always possible to predict who will attain fusion and who will not. Some cases can be treated only for cosmetic reasons from the beginning, this being especially true in older people. In these cases the time of operation is of little importance from a medical standpoint except for psychologic reasons. Of all patients treated, roughly 50 per cent attain fusion. In selected cases this figure is higher. If treatment were started early enough on all patients and full cooperation were received, the overall percentage would be higher. In practically all cases cosmetic improvement can be effected. However, fusion is the factor that holds the eyes straight and if it is not developed, some eyes will deviate again in later years. Deviation which appears later in life will never be as bad as it would have been without surgery, provided proper surgical procedure was followed. A second operation can be done in later years if indicated.

By having a working knowledge of the overall problem of strabismus, the general practitioner and the pediatrician are in a good position to help the patient and advise the parents. Patients should be referred to the ophthalmologist when the condition is first noticed. I prefer to examine any child who shows a large deviation from early infancy by the time he is 12 to 18 months of age. For a great many no treatment will be instituted this early, but the refractive error can be determined and the angle of deviation measured, so that the progress can be followed. If the squint does not appear until later in life, the patient should be referred as soon as it appears.

Let me briefly give my routine in handling these patients. At the first visit an attempt is made to measure the deviation, check the action of the individual muscles, and measure the near point of convergence. If the child is old enough, visual acuity is checked. The parents then are instructed in starting an atropine schedule, which consists of instilling atropine in each eye three times daily for three days. The child is seen again and a refraction is done. All that is necessary for an objective refraction is that he look at the retinoscope light, and a child of almost any age will do so. If there is a significant refractive error, glasses are given and occlusion started if indicated. Measurements are again done one month after constant wear of the glasses. If there is no improvement, surgery is considered. If glasses help to cure the condition, or if the measurement of the deviation is not constant, the child is observed and surgery delayed until it seems indicated.

SUMMARY

Present-day terminology and basic concepts of the anatomy, physiology and etiology involved in eye deviations are reviewed.

It is emphasized that in heterotropia, six facts should be considered when determining the cause and appropriate treatment: (1) What was the time of onset? (2) Is the deviation constant or intermittent? (3) Is the amount of deviation fixed or variable? (4) Is the deviation monocular or alternating? (5) Is there a vertical element present? (6) Is the deviation concomitant or paretic?

Treatment by glasses, exercises, and/or surgery is discussed.

Reasons for the importance of making referral to an ophthalmologist as soon as the condition is observed are given.

The author's routine in handling patients with strabismus is described.

REFERENCES

1. Hay, I.: On Etiology and Prevention of Convergent Concomitant Squint, Tr. Ophth. Soc. U. Kingdom *42*:147, 1922.
2. Lancaster, W. B.: Terminology, Strabismus Ophthalmic Symposium, St. Louis, C. V. Mosby Co., 1950, p. 161.
3. Post, L. T.: Personal communication to the author.
4. Post, L. T.: Suggestions for Surgical Management of Strabismus, Am. J. Ophth. *32*:345-350 (March) 1949.
5. Scobee, R. G.: Oculorotary Muscles, St. Louis, C. V. Mosby Co., 1947.
6. Scobee, R. G.: Anatomic Factors in Etiology of Heterotropia, Am. J. Ophth. *31*:781-795 (July) 1948.
7. White, J. W.: Hyperphoria; Diagnosis and Treatment, Arch. Ophth. *7*:739-747 (May) 1932.

TREATMENT OF LACRIMAL DRAINAGE SYSTEM DISORDERS

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IN the study of ophthalmology, the phase pertaining to the lacrimal drainage system remains the most neglected. This holds true both as to diagnosis and to treatment. Many residents who are finishing their training complain that this segment of their training has been neglected. In many of our large training centers external dacryocystorhinostomies are seldom, if ever, performed. It is true that this operation, as well as the other operations upon the tear drainage system, is not easy, and the end results are not always perfect. Some of the most grateful patients, however, are those who have been relieved of epiphora with its accompanying infection.

Read before the Section on Eye, Ear, Nose, and Throat, Texas Medical Association, Annual Session, Houston, April 28, 1953.

The diagnosis of obstruction of the nasolacrimal duct usually can be made simply. The patient invariably will give a history of epiphora. Fluid cannot be lavaged through the canaliculi into the nose. If there is much infection of the sac, purulent material often can be expressed by pressure over the tear sac. Injection into the tear sac of a radiopaque material such as Lipiodol is advisable, especially in doubtful cases.

TREATMENT

Infants and Children—A surprising number of infants with epiphora have a purulent dacryocystitis. Pus can be expressed by pressure over the tear sac. These infants should have the tear sacs probed, re-

gardless of age, as soon as the diagnosis is made. Epiphora in infants without demonstrable pus in the tear sac can be treated, if desired, by pressure over the sac, as well as by the use of mildly antiseptic drops, until the patient is about 6 months of age. The probe should always be greased before passage, a point frequently ignored.

Often, children who have epiphora have had repeated probings without any relief. It is in these patients, especially, that polyethylene tubing[4] works well. It is inserted through a special thin-walled needle with a blunt-ended stylet.

Adults.—Adult patients with stenosis of the nasolacrimal ducts of relatively short duration, that is, less than two years, usually respond well to the use of polyethylene tubing. Tear sac infection of long standing, especially if a large mucocele is present, probably should have a dacryocystorhinostomy rather than treatment with more conservative measures.

Dacryocystorhinostomy.—Only a few salient points concerning a dacryocystorhinostomy will be considered. In adults there is far less bleeding and the operation is less difficult when done under local anesthesia. The incision should be started just below and about 3 mm. medially to the inner canthal ligament and carried downward for about 1 inch. With large, distended mucoceles, the tear sac occasionally may be opened accidentally with this incision, but no harm is done if this happens. The incision placed in this position will usually miss the angle vessels. Vessels in this position are difficult to tie. Touching the hemostat with the point of the diathermy needle, with the patient grounded, easily closes off the vessels.

The size and position of the bony opening are important. It should be placed anteriorly and inferiorly. This means removing much of the ascending process of the maxilla, which is heavy bone. Removal of this bone with a drill, such as a dental drill, is much easier than with a hammer or chisel. The bony opening should be large, in order that there will be as large an anastomosis as is practical. A large anastomosis is not so prone to late closure as is a small anastomosis. Also, the larger the bony opening, the more nasal mucosa is available with which to fashion mucous membrane flaps. This is especially important when dealing with relatively small tear sacs. Here, there is only a small amount of sac mucosa available with which to fashion flaps. Most of the flaps can be fashioned with nasal mucosa when the bony opening is large.

Ectropion.—Small degrees of ectropion of the lower punctum sometimes can be helped by making four or five small diathermy puncture points on the inner fourth of the conjunctival side of the lid. In more marked senile ectropion, the Kuhut-Szymanowski[2] operation is a satisfactory procedure and is relatively easy to perform. Lee[1] has devised a procedure to correct any residual ectropion of the punctum after a Kuhut-Szymanowski operation. I have used this procedure with a fair degree of success.

Partial Stenosis of Lower Canaliculus.—Complete stenosis of the lower canaliculus is an exceedingly difficult problem for which there is yet no completely satisfactory solution. I have used a polyethylene tubing[4] inserted through a special thin-walled needle with a sharp-pointed stylet. This was left in place for an indefinite period. Many of the patients would get marked relief from epiphora, but the tubing would have a tendency to slip out and sometimes cause local irritation. Theoretically, the Stallard[3] operation is an ideal procedure. From a practical standpoint there are many difficulties. Many of the completely stenosed canaliculi have resulted from injuries, and often there are scars in and around the tear sac also. Another difficulty is the fairly marked tendency toward closure of the new opening of the sac into the lacrimal lake.

In order to better insure patency, I insert a large polyethylene tube (2 or 3 mm. in diameter) through the new opening, down into the nose, and cut it off flush with the conjunctiva. It would seem, with tubing of this size in place, that the patient would have little tearing, but, unfortunately, some tearing persists until the tubing is removed in about three months. Even after the tubing is removed, it is well to observe the patient and perhaps keep the new tear sac opening dilated with a large Bowman probe.

SUMMARY

Careful examination of the lacrimal drainage system will reveal many of the disturbances that might be present. Many of these can be corrected satisfactorily. Although dacryocystitis is annoying to a patient, the results of a properly executed dacryocystorhinostomy usually are gratifying. The type of skin incision, hemostasis, size and position of the bony opening, and the use of membrane flaps have been discussed.

Ectropion and stenosed canaliculi are frequent causes of epiphora and often can be treated successfully. A procedure for the insertion of large polyethylene tubing into the tear sac to insure its patency after a Stallard operation has been described.

REFERENCES

1. Lee, O. S.: Operation for Correction of Everted Lacrimal Puncta, Am. J. Ophth. *34*:575-578 (April) 1951.
2. Spaeth, E. B.: Principles and Practice of Ophthalmic Surgery, ed. 3, Philadelphia, Lea and Febiger, 1944.
3. Stallard, H. B.: Operation for Epiphora, Lancet *2*:743-744 (Dec. 14) 1940.
4. Veirs, E. R.: Nonsurgical Repair of Strictures of Lacrimal Drainage System, A. M. A. Arch. Ophth. *47*:71-75 (Jan.) 1952.

PRESENT STATUS OF CORNEAL TRANSPLANTATION

LOUIS DAILY, JR., M.D. and RAY K. DAILY, M.D., Houston, Texas

CORNEAL transplantation is an operation in which healthy heteroplastic, human corneal tissue is used to replace opaque or inflamed cornea. Opaque cornea is replaced by a corneal transplant to improve vision. Inflamed cornea is replaced as a therapeutic measure, although vision may not be increased by the operation.

If improved vision is the aim of corneal transplantation, a graft which includes the full thickness of the cornea is used. In some inflammatory conditions of the cornea, it is possible to excise the inflamed area by removal of superficial layers of the cornea only. The latter are replaced by a lamellar corneal transplant. Lamellar corneal transplantation usually does not produce good vision, but is less hazardous than penetrating corneal transplantation.

Until recently, corneal transplantation was an unusually hazardous operation, even when performed by experienced, fully qualified surgeons. Stansbury[7] in 1950 analyzed all cases of corneal transplantation done at Columbia Presbyterian Hospital in New York City and concluded that in 13 per cent of the cases vision was improved but that in 35 per cent vision was made worse by the operation, and in many cases the operation resulted in total blindness. Since that time, improvement in instrumentation and surgical technique have improved greatly the prognosis for good vision after corneal transplantation and have reduced markedly the incidence of postoperative complications which formerly threatened loss of all sight.

Of these complications, the most serious was glaucoma. Glaucoma was secondary to adhesion of the iris to the margin of the wound. Adhesion of this kind resulted from delay in reformation of the anterior chamber, or to postoperative rupture of the wound with loss of the anterior chamber. Absence of the anterior chamber was a frequent complication because the transplant was held in position by sutures which overlapped it but did not close the wound tightly. Adhesion of the iris to the wound and glaucoma which followed prolonged absence of the anterior chamber were serious complications because the transplant often became opaque, and glaucoma was often intractable and finally caused blindness.

These complications have not been encountered by us when we used a technique of partially penetrating corneal transplantation which includes the following technical features: maintenance of miosis; intravenous administration of curare; application of egg membrane over the cornea after completion of sutures; topical application of cortisone to the eye at surgery and postoperatively; and placement of multiple simple sutures between the edge of the transplant and the cornea of the host. Sutures are placed in the transplant, and the transplant is sewed directly to the cornea of the host with very sharp needles; these needles have been manufactured only in recent years. Without these needles, sutures could not be placed in the transplant without producing excessive trauma. Multiple simple sutures of the transplant to the cornea of the host with the aid of a sharp needle affords firm and tight closure of the wound and prevents hazardous complications.

Other complications of corneal transplantation

FIG. 1a. Photograph of an eye with keratoconus depicting opacification of the corneal apex.

b. and c. Front (*b*) and oblique (*c*) views of the same eye after corneal transplantation was performed.

Read before the Section on Eye, Ear, Nose, and Throat, Texas Medical Association, Annual Session, Houston, April 29, 1953.

accounted for failure of the transplant to remain transparent in many cases. One of these complications was invasion of the transplant by blood vessels, followed by opacification. Another of these complications was edema of the transplant, which developed weeks after corneal transplantation and ended with permanent opacification. This type of edema is thought to be due to an allergic reaction between donor and host cornea. It was called "maladie de la greffe" by French surgeons because they encountered it frequently.[6] Severe iritis was another complication which occurred after most corneal transplantations.

All three of these latter complications of corneal transplantation—vascularization, edema of the transplant, and iritis—are inhibited by cortisone, and cortisone is applied topically to the eye preoperatively as a part of the technique of corneal transplantation we presently use.

With the surgical risk greatly reduced by this technique, indications for corneal transplantation may be broadened to include many more eyes with poor vision than would have been considered acceptable for corneal transplantation by older techniques. We believe that corneal transplantation by the technique which we have used is indicated for almost any eye with keratoconus in which there is a possibility of improvement in vision after surgery, if visual acuity is 20/60 or less with contact lenses, and visual acuity is not adequate for the patient's needs. With visual acuity of 20/60, a person cannot read ordinary fine print and cannot pursue many occupations. In addition, the necessity for wearing contact lenses can be eliminated by corneal transplantation in many cases of advanced keratoconus.

With older techniques, some ocular diseases have offered a more favorable prognosis for corneal transplantation than others. The disease which has been considered most suitable for corneal transplantation is keratoconus.[1, 4, 5] Corneal dystrophies, except for epithelial and endothelial dystrophy of Fuchs, afford a favorable prognosis.[3] Scar of the central portion of the cornea, the residue of corneal ulcer, also is favorable, even though moderately vascularized. Corneas which are nebulous and vascularized after syphilitic interstitial keratitis are favorable.

Corneas which have been burned by caustic have been considered to be unsuitable for corneal transplantation. Endothelial and epithelial dystrophy of Fuchs has had a poor prognosis.[3, 8] One eye with this dystrophy has been reported to have undergone successful corneal transplantation by a technique similar to the one described herein.[8] Totally leukomatous corneas also have had a poor prognosis, but Castroviejo[2] has reported successful total corneal transplantations by a technique similar to the one we use. Aphakic eyes have had a poor prognosis, although corneal transplantation has succeeded in a small percentage of such eyes.

Data on the results of corneal transplantation by newer techniques have not been assembled as yet for

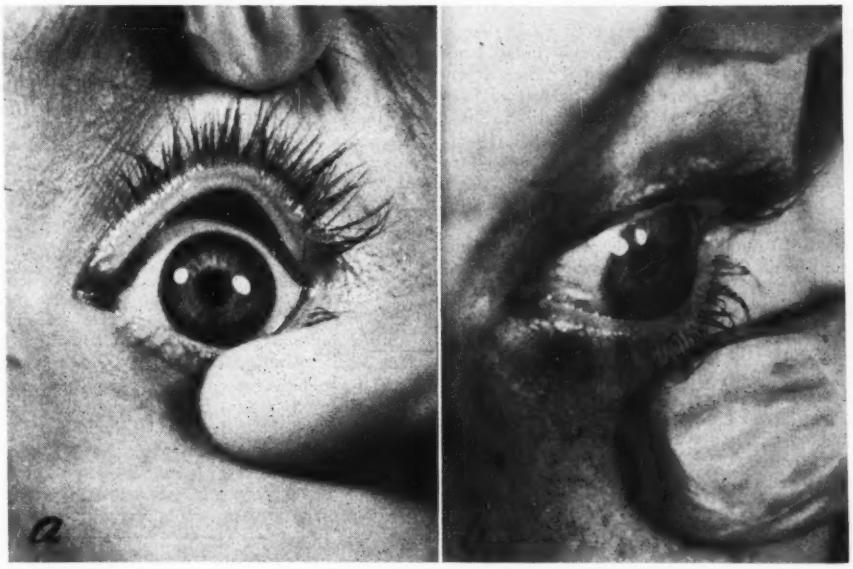

FIG. 2. Photograph of an eye with keratoconus after corneal transplantation was done: *a*, front view and *b*, oblique view.

these diseases. An accurate prognosis for opacities of various etiologies after corneal transplantation is not available, because statistics which were based on older techniques are no longer valid.

CASE REPORTS

The following cases are illustrations of what may be accomplished by corneal transplantations.

A 48 year old woman had advanced corneal dystrophy, which in morphology resembled that described by Groenouw. Visual acuity of each eye was poor. She could recognize only motion of figures nearby and in unfamiliar surroundings had to be led about. Her vision had been at this level for fifteen years, although vision had started to fail thirty years before. An iridectomy had been done many years ago by another physician in the hope of improving vision of the left eye, but it had not had the desired result. Corneal transplantation was done on the right eye in June, 1951, and visual acuity is 20/20.

An 18 year old boy suffered from poor vision due to keratoconus (fig. 1a). Visual acuity through contact lenses was 20/400 for the right eye and 20/90 for the left eye. Corneal transplantation was done on the right eye in January, 1951, and on the left eye in August, 1952. Visual acuity of the right eye with contact lens is 20/30 (fig. 1b and c); visual acuity of the left eye with spectacle lens is 20/40.

A girl age 16, because of keratoconus, had to wear contact lenses in order to have visual acuity of 20/40 for the right eye and 20/50 for the left eye. However, she did not wear the contact lenses and had missed a year of high school because of poor vision. Corneal transplantation was done on the left eye in December, 1951. Visual acuity is 20/30 through a spectacle lens of low power. She reads and has resumed school work (fig. 2).

A 49 year old woman suffered from keratoconus. Even with the aid of contact lenses, visual acuity was 20/60 for the right eye and 20/50 for the left eye. Corneal transplantation was done on the right eye in December, 1951. Visual acuity of this eye through a contact lens is 20/15.

A boy aged 16 had suffered loss of vision of the right eye because of recurrent severe corneal ulceration. Visual acuity was reduced to 20/400 by a corneal scar. Corneal transplantation was done in March, 1952. Visual acuity is 20/30 through a spectacle lens of low power, and binocular vision has been restored.

A woman suffered loss of vision of the right eye because of lipoid dystrophy of the cornea. Visual acuity was reduced to 20/200. Corneal transplantation was done in August, 1952, and visual acuity is 20/20 through a spectacle lens of low power.

SUMMARY

Until recently, corneal transplantation was an unusually hazardous operation. Recent improvements in instrumentation and technique have greatly reduced the risk to the eye and have increased the prognosis for good vision after corneal transplantation. Seven cases in which there was decided improvement in vision following corneal transplantation are discussed.

REFERENCES

1. Castroviejo, R.: Indications and Contraindications for Keratoplasty and Keratectomies, Tr. Am. Ophth. Soc. *43*:324-330 1945; also, Am. J. Ophth. *29*:1081-1088 (Sept.) 1946.

2. Castroviejo, R.: Total Penetrating Keratoplasty (Preliminary Report), Tr. Am. Ophth. Soc. *48*:297-312 (1950).

3. Meller, J.: Ophthalmic Surgery, ed. 6, New York, Blakiston Company, 1953, p. 389.

4. Owens, W. C., and others: Symposium: Corneal Transplantation; Results, Am. J. Ophth. *31*:1394-1399 (Nov.) 1948.

5. Roberts, J. E.: International Symposium on Corneal Surgery; Statistics on Results of Keratoplasty, Am. J. Ophth. *33*:21-23 (March, Part 2) 1950.

6. Sourdille, G. P.: International Symposium on Corneal Surgery. Complications of Penetrating Keratoplasty; Their Prevention and Treatment, Am. J. Ophth. *33*:17-21 (March, Part 2) 1950.

7. Stansbury, F. C.: Corneal Transplantation; Visual and Cosmetic Results, Arch. Ophth. *42*:813-844 (Dec.) 1949.

8. Stocker, F. W.: Successful Corneal Graft in Case of Endothelial and Epithelial Dystrophy, Am. J. Ophth. *35*:349-352 (March) 1952.

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ABSTRACT OF DISCUSSION

DR. OSCAR MARCHMAN, JR., Dallas: This paper presents a profound dissertation on corneal transplantation, and from it much knowledge can be gleaned. Although this type of surgical procedure is not widely used today, it is recognized that more corneal transplantations can be expected to be performed in the future.

I have seen one of the patients in whom a cornea was grafted by the Dailys and can testify as to the good results. There are several points in this paper worthy of discussion.

It is noted that in the technique discussed, the patient's eye was trephined before the graft was taken from the donor eye. This may aid in keeping the transplant clear, but some insurance is needed against accidents such as once occurred in a hospital when the graft was dropped to the floor and the operator was presented with the task of suturing the old cornea back into place. I would think the danger would be less and time would be saved if the graft from the donor eye was removed before trephining the diseased cornea.

One other item of caution should be mentioned. In some instances the donor graft has been inserted and sutured into place with the endothelium on the outside. The results were unsatisfactory, as one can imagine.

The anesthesia, as described, seems adequate, but in the highly nervous patient and in the young patient, it seems that Sodium Pentothal would be indicated.

I believe that air should be used at the close of surgery to restore the anterior chamber. Some inject it at the edge of the graft, while others use the slanting corneal opening made prior to trephining.

World Medical Education Conference

The first World Conference on Medical Education was held in London, England, August 22-29 under the auspices of the World Medical Association in collaboration with the World Health Organization, the Council for International Organizations of the Medical Sciences, and the International Association of Universities. The theme was undergraduate medical education.

Four section sessions were given August 25-27 on the following topics: requirements for entry into medical schools (with the main address by Dr. Victor Johnson of the Mayo Foundation, Rochester, Minn.), aims and content of the medical curriculum, techniques and methods of medical education, and preventive and social medicine.

Such social events as receptions, excursions to Cambridge and down the River Thames, luncheons, and banquets were part of the program.

The opening plenary session August 24 included addresses by Sir Lionel Whitby, president of the World Medical Association; Sir Richard Livingstone; Dr. John Fulton; and Col. S. M. K. Mallick.

OCULAR PEMPHIGUS

HAROLD BEASLEY, M.D., and THOMAS L. SHIELDS, M.D.,
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Discussions of pemphigus in the ophthalmic literature have been few and limited primarily to case reports. In 1942, Klauder and Cowan[2] presented the first comprehensive report, in which they attempted to define and describe the entity and differentiate it from other conditions which previously had been called "ocular pemphigus." Lever[3] recently has considered the whole subject of pemphigus in a comprehensive essay which certainly will clear our thinking about the subject. He divided the entity into two forms, (1) true pemphigus and (2) pemphigoid, the latter of which includes the condition previously considered as "ocular pemphigus."

The ocular manifestations of this disease usually are seen in later life. The incidence varies, but is estimated to be about one in twenty thousand eye cases. Certainly it is not seen often, except in some of the larger teaching centers.

Initial symptoms are irritation, redness, and some secretions. The disease appears as a mild, acute catarrhal conjunctivitis. Later small white bands may be seen under the bulbar conjunctiva, and occasionally small vesicles are present. These are usually fleeting. Ptosis may occur relatively early, and this is associated with symblepharon as a result of scar tissue formation. The palpebral conjunctiva unites with the bulbar conjunctiva, and ankyloblepharon is the result. There is a tendency for the upper lids to be united with the lower lids at the canthi, serving to obliterate the canthi and shorten the horizontal palpebral apertures. This is a characteristic feature of the condition in the late stages. The cornea is damaged by three processes: (1) lack of tears and secretions as a result of destruction of the glands, (2) trichiasis, and (3) pannus formation. It is the corneal damage which leads to blindness, and in the end stages, the cornea may be covered with a skinlike, horny membrane. Corneal ulcers are a common complication. Pain may be severe and intractable and enucleation is sometimes necessary. The inflammation of the conjunctiva may become arrested spontaneously at any time, but in most cases it ends in blindness if the patient lives long enough. The oral mucous membranes are usually involved, and scarring may be absent, but it is always present in the conjunctiva.

Differential diagnosis in the early stages is difficult; the condition is usually confused with an ordinary conjunctivitis. Various types of erythema multiforme, such as Stevens-Johnson disease, must be considered. Conjunctival burns and other traumatism can be ruled out from the history. Ocular pemphigus is most often confused with trachoma and actually may require some observation and study for inclusion bodies to differentiate the two. Trachoma does not produce the marked symblepharon apparent in ocular pemphigus. In the late stages, the clinical picture is characteristic, and once a case has been seen, it is seldom mistaken again.

The bacteriology of ocular pemphigus has been studied and it is obscure. Secondary invaders are always present.

Pathologic changes in ocular pemphigus have been reported in the ophthalmic literature by Klauder and Cowan,[2] Selby and Parisi,[5] Rycroft,[4] Corboy,[1] and Smith, Myers, and Lamb.[6] The changes described by these authors are all late and consequently do not give much information as to how the disease begins. Most of the specimens examined showed chronic inflammation of the subepithelium and lymphoid tissue of the conjunctiva. The epithelium is thickened and sends course pegs into the subconjunctival tissue. The epithelium of the conjunctiva is transformed into epithelium of the malpighian type, in which there is epidermitization without keratinization. Lever[3] described true pemphigus which is characterized by acantholysis and intraepidermal bullae formation. This entity includes (1) pemphigus vulgaris malignus, (2) pemphigus vegetans, (3) pemphigus foliaceous, and (4) pemphigus erythematosus. He also described pemphigoid, which is characterized by an absence of acantholysis and bullae which are subepidermal. Pemphigoid consists of (1) bullous pemphigoid and (2) benign mucous membrane pemphigoid. So-called ocular pemphigus is a manifestation of benign ocular pemphigoid. Klauder and Cowan[2] stated that the pathologic changes in this disease did not compare with those of pemphigus vulgaris and pemphigus foliaceous, but Lever[3] presented the specific differences and actually showed how they are two different entities pathologically and clinically. This information previously had not been brought out in the ophthalmic literature.

Table 1, outlining the diagnostic differences, is reproduced from Lever's[3] works.

Read before the Section on Eye, Ear, Nose, and Throat, Texas Medical Association, Annual Session, Houston, April 29, 1953.

Treatment of ocular pemphigus is controversial. Corboy[1] thought his case was benefited by hydrosulfosol. No other investigator mentions this. Prior to the availability of ACTH and cortisone, there was no treatment other than palliative. These drugs definitely help true pemphigus, but there is some question of their value in pemphigoid, particularly benign mucous membrane pemphigoid. In the late stages after scarring has become profound, apparently no drug is of value.

CASE REPORT

CASE 1.—R. B., a white man, aged 60, was admitted to City County Hospital, Fort Worth, October 30, 1951, complaining of poor vision for the past five months and a painful left eye for the past two weeks. He had been treated by another doctor prior to this. The diagnosis was trachoma stage 4, with perforating corneal ulcer in the left eye and acute conjunctivitis of both eyes. Vision in the right eye permitted counting fingers at 14 feet; the left eye distinguished hand motion at 14 feet. A routine serologic test for syphilis revealed a positive blood Kahn reaction of 32 units. Cultures of conjunctival scrapings were reported "no growth." Examination for inclusion bodies was not available. The patient was treated with sulfacetamide and Aureomycin locally and was given 6,000,000 units of penicillin for his syphilis. The ulcer was treated conservatively, and the anterior chamber reformed in three days with a small anterior senechia. No pannus was seen at this time, but the corneas and conjunctival sacs were dry. There were symblepharon above and below both eyes, and the lids were beginning to adhere at the canthi. The patient was discharged November 15 and was readmitted December 4 for a Kuhnt-Zymanowski procedure of the left lower lid. On April 15, 1952, a modified Ewing procedure was done for trichiasis of the left upper lid. September 8 a diagnosis of ocular pemphigus was made and the patient was given 40 units of ACTH four times daily for one week, and 25 units twice daily for one week. Cortone was used locally for four weeks, but no improvement was shown. The patient was seen by Dr. Alfred Cowan on October 12, and he confirmed the diagnosis. Vision at this time permitted the counting of fingers at 14 feet by the right eye and discernment of hand motion by the left.

The patient was readmitted to the hospital December 17, with herpes zoster ophthalmicus of the frontal branch of the ophthalmic division of the trigeminal nerve. Drying lotions and roentgen ray applied to the gasserian ganglion resulted in relief of symptoms and clearing of skin lesions. On January 25, 1953, the right eye could distinguish hand motion at 2 feet, and the left eye perceived light. The left cornea was heavily vascularized, cloudy, and dry. The right cornea was moderately vascularized and cloudy. A faint red reflex with the ophthalmoscope was seen in the right eye, and no red reflex in the left. Symblepharon was almost complete in both eyes, and the palpebral fissures were very narrow. A biopsy specimen was examined by Dr. Charles Ashworth. He reported as follows: "The histologic changes of this conjunctival tissue are in the nature of a mild, diffuse inflammatory reaction, with epithelial hyperplasia and keratinization. Regarding the possibility of pemphigus of the conjunctiva, it is noted that bullae are missing, although in pemphigus of the conjunctiva, bullae are only rarely present. The keratinization of the epithelium, the inflammatory reaction of the underlying connective tissue, and increased vascularity are compatible with ocular pemphigus; but the finding here cannot be diagnostic in my opinion."

TABLE. 1.—*Differential Diagnosis Between Pemphigus Vulgaris Malignus and Bullous Pemphigoid.*

	Pemphigus Vulgaris Malignus	Bullous Pemphigoid
Type of bulla	Flaccid, usually small	Tense, often large
Erosions	Large, due to peripheral extension	Small, due to lack of peripheral extension
Healing of erosions	Little tendency to healing	Good tendency to healing
Incidence of onset with oral lesions	62 per cent	9 per cent
Incidence of oral involvement	100 per cent	34 per cent
Degree of oral involvement	Severe	Mild
Involvement of the vermilion border of the lips	Common	Very rare
Jewish race	62 per cent	7 per cent
Average age of onset	54 years	66 years (in adults)
Occurrence in childhood	No	Yes
Mortality (before corticotropin and cortisone)	All ages: 94 per cent; up to 65 years: 93 per cent	All ages: 24 per cent; up to 65 years: 0 per cent
Histology of cutaneous and oral lesions	Acantholysis: intraepidermal, usually suprabasal bullae	No acantholysis; subepidermal bullae
Serum chemistry		
Albumin	Considerably decreased	Slightly decreased
Sodium	Considerably decreased	Normal or slightly decreased
Chlorides	Considerably decreased	Normal or slightly decreased

After Lever, W. F.: Pemphigus, Medicine *32*:30 (Feb.) 1953.

Dr. Walter Lever examined a slide and reported that most likely this was ocular pemphigoid. His opinion was based more on the case report than on the histologic section.

SUMMARY

So-called "ocular pemphigus" is really a pemphigoid reaction and is different pathologically and clinically from true pemphigus. It is relatively rare, and the treatment is unsatisfactory. A case of ocular pemphigus is presented.

REFERENCES

1. Corboy, P. M.: Ocular Pemphigus; Report of Classical Case, Am. J. Ophth. *34*:1561-1564 (Nov.) 1951.

2. Klauder, J. V., and Cowan, A.: Ocular Pemphigus and Its Relation to Pemphigus of Skin and Mucous Membranes, Am. J. Ophth. *25*:643-662 (June) 1942.

3. Lever, W. F.: Pemphigus, Medicine, Vol. 32, No. 1, Feb., 1953.

4. Rycroft, B. W.: Ocular Pemphigus, Brit. J. Ophth. *18*:571-578 (Oct.) 1934.

5. Selby, G. D., and Parisi, P. J.: Ocular Pemphigus, Report of Case, Arch. Ophth. *43*:238-243 (Feb.) 1950.

6. Smith, R. C.; Myers, E. A.; and Lam, H. D.: Ocular and Oral Pemphigus, Arch. Ophth. *11*:635-640 (April) 1934.

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ABSTRACT OF DISCUSSION

DR. THOMAS L. SHIELDS, Fort Worth: This entity is rare, and I would like to reiterate some of the differential

OCULAR PEMPHIGUS—Beasley & Shields—*continued*

diagnostic criteria pointed out in the paper. My remarks are made after reviewing the literature and are not from personal experience.

The diagnosis of ocular pemphigus is extremely difficult, especially in the early stages. As has been pointed out, the diagnosis is most often confused with trachoma. The ophthalmologist is in a better position to make this differentiation than the dermatologist. Late stages of xerosis, caused by severe vitamin A deficiency, may simulate early ocular pemphigus. Stevens-Johnson syndrome, which is severe erythema multiforme with bullous lesions of the conjunctiva, also involves other mucous membranes with associated constitutional symptoms. Late stages of scarring of Stevens-Johnson syndrome, as a differential diagnostic point, may be more difficult.

In ocular pemphigus, the vesicle or bullous lesion is seldom seen. Klauder and Cowan reported 1 of their 11 cases to present this finding. Pemphigus vulgaris may affect the palpebrae and bulbar conjunctiva, but usually there are other manifestations, such as bullae on the skin and painful superficial erosions of the mouth and genital area. The patient is ill.

The histologic differences of bullous pemphigoid and true pemphigus has been shown in the table. The main difference is the subepidermal bullae that exist in benign mucous membrane pemphigoid compared to the intraepidermal vesicles of pemphigus. Pemphigus vulgaris is a superficial lesion. Civatte, in 1943, described acantholysis of epidermal cells in true pemphigus. There is a loss of intercellular bridges, and this finding is the basis of the Tzanck test.

The Tzanck test consists of scraping the base of a ruptured bullous lesion. The fluid is placed on a slide and stained with Giemsa's stain. This shows acantholysis in true pemphigus, but not in benign mucous membrane pemphigus.

Two interesting findings occurred in the case reported. The patient had a positive serologic test for syphilis, yet the pathologic and clinical picture was not that of syphilis. He received adequate treatment with no clinical response. A spinal fluid examination was negative. Too, he developed herpes zoster after ACTH therapy. The frequency of occurrence of this phenomenon is more than coincidence.

Evaluation of Recent Developments in Neuro-Otologic Diagnosis

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HENRY A. BROWN, M.D., Rochester, Minnesota

THE production of nystagmus by application of hot and cold stimuli to the labyrinths long has been known. By means of a technique consisting of a series of minimal constant warm and cool stimuli to the labyrinths and interpretation of the response patterns, it is claimed that information may be obtained which is of value in lateralizing temporal lobe tumors. It is implied that, since only temporal lobe tumors cause a change in the response patterns, it may be of some specific diagnostic value. This study was undertaken in an effort to evaluate the usefulness of this proposed diagnostic aid.

Nystagmus-bereitschaft was described by Kobrak[10] during the period from 1918 to 1922. It is a phenomenon, as the name indicates, of nystagmus readiness or preparedness and is also called nystagmophilia. It is a state of centrally increased excitability of the vestibular system. Kobrak carried out experiments in which threshold or near threshold caloric stimuli were applied to the right and left ears until the summation of right-left-right stimuli brought about an effect which could be localized centrally—the direction of the nystagmus produced being irrelevant.

Bauer and Leidler[1] described a change in the postrotary nystagmus tendency in rabbits following the removal of one cerebral hemisphere. It was found that the cessation of rotation toward the side of the intact hemisphere caused a brisker nystagmus than that which followed cessation of rotation to the side operated upon. Dusser de Barenne and de Kleyn[4] confirmed these experimental findings. However, by carrying the investigation a little further and stimulating both labyrinths with hot and cold water, they were able to demonstrate that this phenomenon was not to be accounted for on the basis of suppression or excitation of one labyrinth or the other (increased sensitivity of the labyrinth on the side of the absent hemisphere) as Bauer and Leidler had suspected, but rather on the basis of a central facilitation of induced labyrinthine nystagmus in a particular direction (to the side of the absent hemisphere). These authors found, for example, that if the left hemisphere were removed, not only did postrotary nystagmus show a directional preponderance to the side operated upon (left), but also that cold water stimulation of the right ear produced a more active and longer nystagmus to the left than to the right when the left ear was so stimulated. In addition, upon hot water irrigation of the canal of the left ear, the nystagmus produced to the left was greater than that produced to the right when similar hot caloric stimuli were applied to the right ear. Thus, it was shown that the phenomenon of Bauer and Leidler was clearly of

Abridgement of thesis submitted by Dr. Anthony to the faculty of the University of Minnesota in partial fulfillment of requirements for the degree of master of science in otolaryngology and rhinology.

Read before the Section on Eye, Ear, Nose, and Throat, Texas Medical Association, Annual Session, Houston, April 28, 1953.

central location and was not merely a simple matter of increased or decreased excitability of one or the other labyrinths.

De Kleyn and Versteegh[9] applied this observation to the study of cerebral tumors. Thirty-six cases were studied by the technique of Kobrak, with hot and cold stimuli being used. Eleven of the group demonstrated this central facilitation of induced labyrinthine nystagmus to the side of the lesion. Unfortunately there is no record of the type or the location of these lesions. Neither is it known whether necropsy material was studied in all cases. One case in which there was a large frontal abscess was described. This case demonstrated directional preponderance to the side of the lesion.

In 1942 the hot and cold water tests were revised by Fitzgerald and Hallpike[6] and applied to the clinical diagnosis of cerebral tumors. The startling result was that of 20 cases of cerebral lesions (proved by clinical findings, surgery, or necropsy reports) directional preponderance of induced labyrinthine nystagmus was present in 10 cases of temporal lobe lesions but not in 10 cases in which the lesions were outside the temporal lobe.

The technique developed by Fitzgerald, Cawthorne, and Hallpike[1a] to "push the resolving power of the caloric tests to their limits" was as follows: The patient lies supine with the head and shoulders elevated 20 degrees with eyes fixed on a convenient mark on the ceiling straight ahead of the eyes. Bartel's glasses are not used. There is no position change during the test and the duration of nystagmus following the beginning of irrigation is the only observation made. Water is delivered to the external auditory canals at the rate of 8 ounces per forty seconds (which is taken as the optimum length of time for irrigation). Water is delivered from douche cans via tubes at temperatures of 30 C. and 44 C. (7 C. above and below body temperature). A single caloric test for directional preponderance consists of four parts: (1) cold water irrigation of the left canal, (2) cold water to the right canal, (3) warm water to the left canal, and (4) warm water to the right canal. After cessation of nystagmus, five minutes is allowed to pass before the next irrigation is begun. One patient requires a little over one-half hour to test, but in groups, 3 or 4 patients can be tested in one hour. Figure 1 shows typical response patterns.

MATERIAL AND METHODS

Using a slightly modified Fitzgerald, Cawthorne, and Hallpike technique, 20 patients suspected of having cerebral lesions in or near the temporal lobe were examined.

The technique of caloric stimulation was the same as that previously described except for the following: The water to be used in the test was kept in thermostat-controlled constant temperature baths and delivered to the external auditory canals by a 50 cc. syringe with a small rubber tube adapter to assure its flow against the tympanic membrane. Each individual stimulus consisted of 50 cc. of water injected into the ear canal over a period of forty seconds timed accurately by an assistant. Large, accurately calibrated mercury thermometers were kept immersed in the water of the constant temperature baths at all times. The temperature water at 44 C. cooled .75 to 1.25 C. in fifty seconds, while water in the syringe and that withdrawn from the 30 C. bath cooled .25 to .50 C. in the same period. Therefore, to correct for this variable, the baths were adjusted to maintain water temperatures of 45 C. and 30.5 C. so that upon reaching the external ear canal the water would have a temperature of within .25 C. of 44 C. and 30 C. respectively.

Two observers to watch the nystagmus endpoint

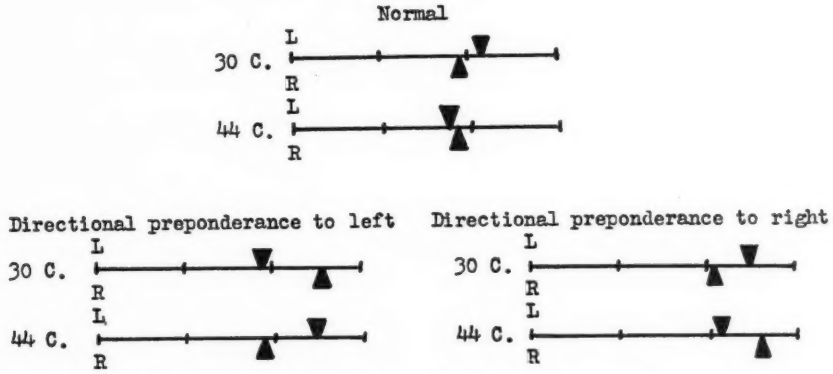

FIG. 1. Typical response patterns in caloric tests for directional preponderance.

were not available. Ordinarily the duration was timed by one observer.

RESULTS

Twenty patients suspected of having temporal lobe lesions were examined by this method. These cases were followed until final disposition was made in an attempt to evaluate the tests as a diagnostic aid and to compare its value with other diagnostic procedures.

Of the 20 patients examined, 14 eventually underwent surgical exploration. Five patients were not operated upon because there was insufficient evidence of an intracranial lesion to warrant exploration. One patient was not operated upon because exploration was not required to establish the diagnosis, and the lesion was not amenable to surgical treatment.

Of the 14 patients in whom surgical exploration was undertaken, 10 proved to have expanding intracranial tumors involving the temporal lobe alone or the temporal lobe as well as other areas of the same hemisphere. Pathologic reports were as follows: 1 glioma of unspecified type; 4 astrocytomas; 2 ependymomas; 1 metastatic small cell bronchogenic carcinoma; 1 malignant meningioma; and 1 psammomotous meningioma. Exploration in 1 case revealed a large intracerebral hematoma secondary to an arteriovenous fistula or an angioma, raising to 11 the number of cases in which exploration actually revealed expanding masses. In 2 cases craniotomy had been done previously and had been followed by a recurrence of the tumor.

In 3 cases in which exploratory surgery was performed tumors were not found. In one a scar was found at the left foot area of the motor cortex. In the second a degeneration of the fronto-temporo-parietal areas probably due to a vascular lesion was found. In the last a tumor was not found, but a decompression was done in the belief that a deep tumor was present in the frontal lobe.

Table 1 gives a summary of all cases studied and includes the tabulation of the diagnostic tests used.

Of the 11 cases in which expanding masses were found (including the intracerebral hematoma, case 11) directional preponderance of induced nystagmus could be demonstrated in all but 2. In 1 case there was no lateralization to either side (case 9). In the other (case 4), a tendency was present but was not sufficient to be called a true lateralization. In this case pressure of the meningioma which arose from the tentorium on the eighth nerve possibly may account for the irregularity. In case 14, in which exploratory surgery was done but no tumor was found, there was no lateralization. In this case a deep frontal tumor was thought to exist. In case 15, in which exploration was done, a scarred area was found in the foot area of the motor cortex. The test did not demonstrate a distinct directional preponderance in this case but was suggestive and probably should be considered a false positive if the test is supposedly specific for temporal lobe tumors. In case 13, exploration revealed fairly extensive degeneration on one side which was thought to be due to a vascular lesion. Lateralization of the directional preponderance was to the opposite side. This constitutes a false lateralization. In a comparable case, number 12, in which surgery was not done, the patient was thought to have a vascular lesion on the right on the basis of polycythemia vera. In this case the lateralization was to the side of the lesion.

In 4 out of 5 other cases of the group in which surgical exploration was not done no directional preponderance was demonstrated. In case 18 directional preponderance was demonstrated to the right. In this case there was a grade 2 delta localization in the temporal region on the right noted on the electroencephalography report. Exploration was decided against and this case must be considered probably false positive, for the time being at least.

In the total group of 20 cases it may be said that there were 2 false negatives and possibly 2 false positives. In the 11 cases in which expanding masses (10 neoplasms proved by exploration and pathologic examination) were found, directional preponderance to the side of the lesion was demonstrated in 9. Visual field studies were done and proved to be reliable in all 11 patients. Electroencephalograms were made in 10 cases. These showed delta localization on the proper side in 9 and were indefinite in 1. Angiograms were done in 2 cases. They did not aid in localization in either case. Air encephalography was done in 3 cases. The side of the lesion was correctly indicated in 2 cases and the study was interpreted as negative in 1 case in which a deep temporal tumor was found two months later.

In all cases roentgenograms of the skull were made and in 3 cases these lateralized the lesion. One showed a shift of the calcified pineal body away from the tumor. In 2 others the lesions themselves contained calcium.

Case 11 was interesting in that there was a perceptive hearing loss on the side of the lesion (left), as well as a suppressed caloric reaction to both warm and cool stimuli. Directional preponderance to the side of the lesion was superimposed. Audiologic examination revealed that the phenomenon of recruitment was not present in the partially deafened ear implying that the hearing loss was not due to end-organ disease as suggested by Dix, Hallpike, and Hood[3] and Eby and Williams.[5] Exploration revealed a large intracerebral hematoma on the left due to arteriovenous fistula or angioma. This accounted for

TABLE 1.—*Summary of 20 Cases in Which Cerebral Lesions in or Near the Temporal Lobe Were Suspected.*

No.	Age, Sex	History and Neurologic Examination	Fields	Air Studies	Angiogram	EEG	Calorigram*	D. P.†	Biopsy	Topography
1	42 M	Chorea in childhood. Two yr. ago began to feel tired all time, occasionally lightheaded. One yr. ago l. hand and leg became suddenly weak, bifrontal headache. Entire l. side numb. This fluctuated but overall picture progressive. Neurologic examination revealed weakness of extremities on l.	Homonomous quadrant defect. L. homonomous hemianopsia later	Reg. interpretation	Neg.	Gr. 1 temp. delta. Normal on repetition later	R 2′ 10″ L 3′ 10″ R 3′ 30″ L 2′ 30″	R.	Gr. 3 glioma	Deep temp.
2	33 F	Psychomotor and grand mal epilepsy for 5 yr. Weakness of r. arm for 3 mo. L. occipital headaches. Homonomous hemianopsia 2 mo. Mentally dull. Increased tendon reflexes on r. Papilledema 1-2 diopters bilaterally.	R. hemianopsia	Not done	Not done	Gr. 3 delta l. temp. spreading to front.	R 2′ 35″ L 2′ 10″ R 2′ 15″ L 2′ 35″	L.	Gr. 3 astrocytoma	Deep l. temp. parietal. Temp. soft.
3	58 M	One yr. ago working on roof, felt faint and fell to ground. No convulsive movements. Since has had 20-25 such episodes. Tremor most of time. R. frontal headache. Slight euphoria & confusion. Reflexes slightly more active on l.	R. homonomous upper quadrant defect. Choked disks.	Not done	Not done	Gr. 2 delta r. front. spreading to temp.	R 1′ 45″ L 2′ 15″ R 2″05″ L 1′ 57″	R.	Gr. 4 astrocytoma. Decomp. done	Temp. fronto-parietal
4	47 F	Frontal headaches. Fainting spells (blackouts) 2-3 times weekly. Increased irritability. Neurologic examination negative.	R. homonomous hemianopsia	Not done; x-ray pineal displacement to r.	Not done	Gr. 2 delta r. temp.	R 2′ 15″ L 1′ 40″ R 1′ 49″ L 1′ 43″	Neg.	Meningioma malignant	Arising from tentorium, filling middle fossa. Found by inc. through temp. convolution
5	27 F	Nine yr. ago had attacks of unconsciousness with numbness & tingling of l. hand. Returned after 9 yr. with "fuzzy vision," severe pressure headache in vertex for past 1 mo. Choked disks. Some incoordination of l. arm & leg with slightly increased reflexes.	Enlarged blind spots with l. homonomous hemianopsia	Not done; x-ray calcium in parietal area	Not done	Indefinite	Not available		Part. calc. cell. ependymoma encap. (3 cm. diam.)	R. parietal
				Not done	Not done	Dysrhythmia always stronger r. temp. Greater r. with hyperventilation	R 2′ 20″ L 3′ 14″ R 2′ 55″ L 2′ 45″	R.	Gr. 2 ependymoma	Same but 5x4x3 cm. diam. pressing on temp.
6	41 M	Attacks of weakness with unconsciousness for 6 yr. During past 3 wk. had several seizures with loss of sphincter control. R. hemiplegia & increased tendon reflexes. Some mental confusion & aphasia.	L. homonomous hemianopsia	Not done	Not done	Gr. 2 r. fronto-temp. delta	R 1′ 40″ L 2′ 25″ R 2′ 35″ L 2′ 10″	R.	Gr. 3 astrocytoma	R. fronto-temp. parietal deep involving temp. horn of lat. vent.
7	38 M	For 2 yr. had several auto accidents & had to quit driving because of difficulty seeing objects on r. Aphasia for 5 mo. One convulsive seizure 2 yr. ago.	R. homonomous hemianopsia. Early choked disks	Positive elsewhere	Not done	Gr. 1 delta l. temp.	R 2′ 15″ L 1′ 55″ R 2′ 03″ L 2′ 30″	L.	Gr. 3 mixed oligo & ependymal cell glioma	Temp., parietal, occipital r.
8	44 M	Transitory numbness of r. side of body. Aphasia marked. Otherwise neurologic examination negative.	R. homonomous lower quadrant defect; small but definite	Not done	Not done	Gr. 3 delta l. front.	R 2′ 05″ L 1′ 50″ R 1′ 50″ L 2′ 00″	L.	Gr. 4 bronchogenic ca "catcell"	Beneath parietal gyrus, sup. temp.
9	50 M	Convulsive disorder for last 2 yr. Unreal sensation during indefinite acute episodes. Severe attack in hospital recently. Drowsy & inattentive. Neurologic examination negative.	Homonomous l. upper quadrant notch	Ventriculogram suggested lesion r. fronto-temp. area	No help	Gr. 2 delta r. fronto-temp.	R 2′ 35″ L 2′ 37″ R 2′ 50″ L 2′ 50″	Neg.	Astrocytoma	R. temp. (large)
10	35 M	Momentary mental dullness for 9 yr. Past 2 yr. has had 30 min. spells of blankness preceded by visual blurring followed by unconsciousness. Dull frontal headache relieved by aspirin. Air encephalogram interpreted elsewhere as old clot. Neurologic examination negative.	Minimal r. upper quadrant homonomous defect	Not done; x-ray pineal pushed to r.	Not done	Delta l. temp. spreading to l. frontal	R 2′ 09″ L 1′ 45″ R 0″ L 1′ 55″	L.	Degen. gliotic brain tissue psammomatous meningioma	Filling middle fossa

TABLE 1.—*Summary of 20 Cases in Which Cerebral Lesions in or Near the Temporal Lobe Were Suspected (Continued).*

No.	Age, Sex	History and Neurologic Examination	Fields	Air studies	Angiogram	EEG	Calorigram*	D. P.†	Biopsy	Topography
11	43 M	Migraine headaches for lifetime with visual aura; then severe pain l. hemicranium persisting until hard emesis. Eight yr. ago had 2 such attacks with loss of consciousness. Wife noted aphasia & wrong answers to simple questions. Two wk. ago headache with emesis & unconsciousness, stiffening of body. Headache persistent since. Aphasia.	R. homonomous hemianopsia	Not done; x-ray calcium les. left occipital region	Not done	Gr. 3 delta l. temp. & frontal	R 2′ 20″ L 0″ R 2′ 07″ L 1′ 30″	L. L. canal paresis	Clotted blood	L. intracerebral hematoma second to arteriovenous fistula or angioma
12	49 M	Weakness & numbness l. hand for 4 wk. Convulsive seizure 7 yr. ago, another 2 yr. ago. Severe bifrontal headache past year. R. hemiplegia.	L. homonomous hemianopsia	Not done	Not done	Gr. l. delta r. temp.	R 2′ 18″ L 2′ 59″ R 2′ 57″ L 2′ 24″	R.		Not explored. Polycythemia vera.
13	64 M	Four mo. ago gradual onset of weakness of l. wrist & hand. Gradually proceeded to l. hemiparesis, some loss of memory & trouble with speech.	L. quadrant homonomous hemianopsia	Mark. shift of vent. nys. to r.	Not done	Not done	R 2′ 13″ L 1′ 55″ R 2′ 13″ L 2′ 18″	Neg. (not definite)	No biop. degen. les. r. fronto-par. temp.	L. front.parieto-temp. cortical degen. convolutions small.
14	54 M	Fronto-occipital headache (only 15 to 20 min. in p. m.). Eyes feel heavy, trouble remembering names. Three fairly typical epileptiform seizures. Unconscious 3 hr. R. partial hemiparesis. Some aphasia, apraxia, ataxia.	Normal	Not done	Not done	Gr. 2 delta to l.	R 2′ 20″ L 2′ 25″ R 2′ 36″ L 2′ 25″	Neg.	Tumor not found. Decomp. done	Tumor not found. Assumed to be deep front. Removed portion mid-front. lobe decomp.
15	27 F	Noticed twitching & drawing of r. leg for 3 wk. Shooting pain in r. toes. True Jacksonian seizures witnessed by examiner. Syphilitic history; treated previously. Normal neurologic examination.	Normal	Not done preop.	Not helpful	Gr. 2 delta l. temp. dysrhythmia. Gr. 2 delta l. parietal	R 1′ 32″ L 1′ 25″ R 1′ 45″ L 2′ 13″	L.	Scar tissue	Scar l. foot area of motor cortex
16	45 M	Headache & back pain. Did not feel recent burn of hand. Hands & legs weak. Neurologic reaction bizarre.	Homonomous hemianopsia by rough fields. Later detailed fields neg. Pt. unreliable.	Not done	Not done	Not done	R 2′ 13″ L 2′ 12″ R 2′ 17″ L 2′ 10″	Neg.	Not explored	Not explored
17	15 M	R. otitis media of 18 days' duration with vomiting. Left-sided convulsion lasting 1 min. followed by sleeping. Responded to dihydrostreptomycin & penicillin, probable embolic focus controlled by antibiotics before abscess formed. Neurologic examination negative at time of caloric test.	Normal	Not done	Neg.	Not spec. Varied change r.	R 2′ 00″ L 1′ 50″ R 1′ 55″ L 1′ 50″	Neg.	Not explored	Not explored
18	65 M	Pain l. eye & l. front. region for 2 yr. Generalized convulsive seizures. Neurologic examination negative.	Normal	Horn left lat. ventr. did not fill	Not done	Gr. 2 delta r. temp.	R 3′ 00″ L 3′ 15″ R 3′ 05″ L 2′ 36″	R.	Not explored	Not explored
19	56 F	Two seizures in past 2 mo. First preceded by buzzing in ears then unconsciousness; then r. hand started shaking. Second time suddenly unconscious. Complained of headache. Neurologic examination negative.	Normal	Neg.	Not done	Gr. 2 delta r. temp.	R 1′ 35″ L 1′ 15″ R 1′ 37″ L 1′ 25″	Neg.	Not explored	Not explored
20	27 M	Blank out spells for 4 yr. Now occur several times weekly. Patient "freezes." Can keep on driving, etc. Incoherent for few minutes after. Last attack severe. Lost consciousness for some time. Normal neurologic examination.	Normal	Ventriculogram neg.	Not done	Gr. 1 delta temp. l.	R 2′ 28″ L 2′ 05″ R 2′ 15″ L 2′ 15″	Neg.	Not explored	Not explored

*First pair of figures for 30 C., second pair for 44 C.

†Directional preponderance.

directional preponderance as well as perceptive hearing loss without recruitment and depressed caloric response. The hematoma was large enough to produce pressure on the eighth nerve.

CONCLUSIONS AND DISCUSSION

A definite tendency of temporal lobe tumors to produce directional preponderance of induced nystagmus to the side of the lesion has been demonstrated, thus confirming the work of Fitzgerald and Hallpike.[6]

The accuracy of the test as well as other diagnostic aids is not beyond question in an individual case. Visual field examinations were the most reliable aid in this group of cases.

Several serious disadvantages present themselves in the use of the test. A spontaneous nystagmus, any weakness or palsy of the external ocular muscles, inadequate cooperation as seen in some of these patients, and middle ear disease, as well as end-organ lesions, exclude completely or partially the efficient use of this test. Further, the brain stem contains many tracts and nuclei which, if injured, will produce a spontaneous nystagmus. It stands to reason, therefore, that various diseases of the central nervous system and its vascular supply may produce minor injuries too small to produce a spontaneous nystagmus but large enough to cause a change in tonus capable of producing directional preponderance of induced nystagmus. For example, consider the case of Clarke[2] in which persistent directional preponderance was found in a case of syringobulbia. Elderly people with arteriosclerotic changes, as well as many other groups, are likely to show directional preponderance in the absence of cerebral lesions. Caloric lateralization of cerebral tumors is not to be considered a means to diagnosis in itself but must be considered in conjunction with other findings.

Accurate timing of the duration of nystagmus is difficult in this test, particularly since relatively small changes in duration in one part can change the response pattern and consequently the interpretation of the findings. Searching movements are sometimes seen before the onset or after cessation of true nystagmus. Glorig and associates[8] have developed an electrical device which provides an objective means, electronystagmography, of recording the duration of nystagmus accurately.

The interesting work of Wycis and Spiegel[12] on directional preponderance, performed some time ago, only recently has found its way into the otolaryngologic literature. This work offers the most rational explanation we have found of the phenomenon of directional preponderance in cerebral lesions.

RECRUITMENT

It would not be fitting to discuss advances in neuro-otologic diagnosis without dwelling shortly on the recruitment phenomenon.

In 1936, Fowler[7] described a method of testing hearing which was said to differentiate neural from conduction deafness without recourse to determination of the thresholds of either bone conduction or air conduction of sound. This test consists of the measurement of the recruitment of loudness with increasing intensity of sound. Fowler first demonstrated the presence of recruitment by balancing the loudness of a sound which was alternately thrown first into one ear and then into the other. This was referred to as the "alternate binaural loudness balance" test.

When Dix, Hallpike, and Hood,[3] in 1948, observed that the loudness recruitment phenomenon was characteristically present in Menière's disease and absent in cases of eighth nerve tumors and lesions at the cerebellopontine angle, they gave new importance to recruitment tests in the differential diagnosis of lesions of the end-organ and nerve fibers which produce deafness.

The same authors, one year later, reported that further observations in 2 cases of Menière's disease and 2 cases of neurofibromas of the eighth nerve revealed differences in the intelligibility of speech associated with the two lesions. They found that in Menière's disease there was a recruitment of loudness but no recruitment of speech intelligibility; on the other hand, in the presence of neurofibromas, speech became more intelligible with increasing amplification up to a point. These findings sharply contradicted previous concepts as to the physiologic mechanism of recruitment.

In the study by Eby and Williams,[5] alternate binaural loudness balance tests were made on 32 patients with unilateral deafness diagnosed as Menière's disease and on 1 patient with unilateral deafness thought to be the result of a vascular accident which involved the organ of Corti. Loudness recruitment was present in every case. In 17 cases there was evidence of overrecruitment.

Alternate binaural loudness balance tests also were made on 16 patients with deafness due to degeneration of nerve fibers. In 8 cases of intracranial lesions which involved the eighth nerve fibers, there was little or no evidence of loudness recruitment.

These findings add further evidence to indicate that loudness recruitment is present in a lesion of the organ of Corti but absent in a lesion of the auditory nerve fibers.

Saltzman[11] has shown in 3 cases of craniocerebral trauma that the recruitment phenomenon was entirely absent. It is probable that the pathologic changes

consist of contusion of the brain with petechial hemorrhages involving the cochlear nuclei. In 1 case the vestibular pathways also were involved. It is possible also that the eighth nerve may be injured as it traverses the temporal bone.

SUMMARY

An evaluation of directional preponderance in the lateralization of temporal lobe tumors was attempted by examining 20 patients suspected of having such a lesion by the Fitzgerald, Cawthorne, and Hallpike technique. It was found that a definite tendency exists for directional preponderance toward the side of the lesion but that in an individual case this sign could not be considered conclusively diagnostic. It was found that the test compares with other diagnostic aids in common use. In the group of 11 expanding masses involving the temporal lobe, the only test that did not give at least one false positive or one false negative was the visual field examination.

The recruitment phenomenon as an aid in differential diagnosis of end-organ, acoustic nerve, traumatic craniocerebral, and impedance lesions has been discussed.

REFERENCES

1. Bauer, J., and Leidler, R.: Ueber den Einfluss der Ausschaltung verschiedener Hirnabschnitte auf die vestibulären Augenreflexe, Monatschr. f. Ohrenk. *45*:937-942, 1911.

1a. Cawthorne, T. E.; Fitzgerald, G.; and Hallpike, C. S.: Studies in Human Vestibular Function; Observations on Directional Preponderance of Caloric Nystagmus (Nystagmusbereitschaft) Resulting from Unilateral Labyrinthectomy, Brain *65*:138-160 (June) 1942.

2. Clarke, T. A.: Observations on Caloric Tests of Vestibular Function, J. Laryng. & Otol. *58*:380-386 (Sept.) 1943.

3. Dix, M. R.; Hallpike, C. S.; and Hood, J. D.: Observations upon Loudness Recruitment Phenomenon, with Especial Reference to Differential Diagnosis of Disorders of Internal Ear and Eighth Nerve, Proc. Roy. Soc. Med. *41*:516-526 (Aug.) 1948; J. Laryng. & Otol. *62*:671-686 (Nov.) 1948.

4. Dusser de Barenne, J. G., and de Kleyn, A.: Vestibular Ocular Reflex, von Graefe's Arch. *111*:374-392, 1932.

5. Eby, L. G., and Williams, H. L.: Recruitment of Loudness in Differential Diagnosis of End-Organ and Nerve Fiber Deafness, Laryngoscope *61*:400-414 (May) 1951.

6. Fitzgerald, G., and Hallpike, C. S.: Studies in Human Vestibular Function; Observations on Directional Preponderance ("Nystagmusbereitschaft") of Caloric Nystagmus Resulting from Cerebral Lesions, Brain *65*:115-137 (June) 1942.

7. Fowler, E. P.: Method for Early Detection of Otosclerosis; Study of Sounds Well Above Threshold, Arch. Otolaryng. *24*:731-741 (Dec.) 1936.

8. Glorig. A., and Mauro, A.: Clinical Electronystagmography, Ann. Otol., Rhin. & Laryng. *59*:146-151 (March) 1950.

9. de Kleyn, A., and Versteegh, C.: Some Remarks upon Present Position of Physiology of Labyrinth, J. Laryng. & Otol. *42*:649-655 (Oct.) 1927.

10. Kobrak, F.: Studies on Vestibular Nystagmus, J. Laryng. & Otol. *58*:167-187 (May) 1943.

11. Saltzman, M.: Recruitment Phenomenon in Craniocerebral Trauma; Report of Representative Cases, A. M. A. Arch. Otolaryng. *52*:782-785 (Nov.) 1950.

12. Wycis, H. T., and Spiegel, E. A.: Effect of Cortical Lesions and Elimination of Retinal Impulses on Labyrinthine Nystagmus, A. M. A. Arch. Otolaryng. *57*:1-11 (Jan.) 1953.

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ABSTRACT OF DISCUSSION

DR. LOUIS E. ADIN, JR., Dallas: The history of vestibular physiology is a long and interesting one. Despite its duration, there is a less complete understanding of the vestibule than its partner, the cochlea. This is true not only because of its greater complexity and central connections, but also because of the difference in reaction to the various stimuli between human beings and the lower animals.

The knowledge and understanding of vestibular function which modern otologists and neurologists enjoy is the result of a great deal of painstaking work. Vestibular physiology is said to have had its beginning with the work of Florens, who published in 1824 his observations on the behavior of pigeons in which he had destroyed the various semicircular canals. Ewald in 1892 published his classic work which was carried out by the ingenious method of compressing the various membranous semicircular canals. To Barany is attributed the scientific approach to vestibular testing by caloric stimulation and rotation. But many lesser known workers employed other methods of testing the labyrinth such as electrical and chemical stimulation. The work of the better known men was preceded by observations on the part of others. For instance, Purkinje in 1820 described vertigo as a result of rotation. And Breuer in 1874 described nystagmus in animals that had been subjected to rotation.

Since the time of Barany, numerous workers have described standardized caloric methods of stimulating the labyrinth and the response, usually measurable nystagmus, is timed. That each test leaves a little something to be desired, however, is manifested by the number of modifications used. Much clinical information can be derived from the application of these tests, but there is still much controversy as to its interpretation.

Why has it been so difficult to delineate and describe completely labyrinthine function? In human beings the sensory perception excited by stimulation of the vestibular apparatus is vague and ill-defined. Factors such as muscle sense and sensations arising from vasomotor disturbances are always present to confuse the picture. Also many reactions, cerebellar, visual stimuli, proprioceptive, and contact, which are similar to labyrinthine reactions must be considered, as well as the fact that these other reactions may arise also from excitation of the vestibular apparatus. In addition, there has yet to be perfectly described and assigned the individual function of the various portions of the labyrinth. As a result, we find ourselves today in the position of having a great deal of valuable information from the various researches, but not yet in the position of being able to consider this information final and infallible.

Fortunately for those of us who are primarily clinicians, there are many men who are not satisfied with what we already know about vestibular function. The fact that we may determine inactivity, hypoactivity, or hyperactivity of a given labyrinth is considered insufficient. These men have continued to ferret out more facts about labyrinthine function. They have not been content with the methods already described for stimulating the labyrinth. In 1942, Fitzgerald, Hallpike, and Cawthorne first published their studies in vestibular function describing the phenomena of canal paresis and directional preponderance. In addition they described a method of stimulating the labyrinth which promises to reduce to a minimum the several factors which lead to errors in application and interpretation. Also they described the interesting phenomenon of directional preponderance to the side of temporal lobe lesions. If their reports can be substantiated, here is one more important clinical application of the results of vestibular testing.

As might have been expected, there were mixed responses to this announcement. There were and are many otologists who are of the opinion that the only information which can be depended upon from labyrinthine stimulation is whether or not a given labyrinth is active. There was not a little resistance to the somewhat unwieldy technique which these workers described for testing the labyrinth. On the other hand, some enthusiasm was stirred up by the possibility that more information can now be derived from caloric stimulation than formerly. As always, there were a few who greeted this work with doubt, and the more generous of them withheld any expression of opinion until the work had been substantiated.

Whether it was due to a lack of interest or time or clinical material, only a few people, mostly in large institutions, have attempted to duplicate the results reported by these workers. Dr. Anthony is one of these exceptional individuals. In his time-consuming and painstaking work, he also has elicited a definite tendency for directional preponderance toward the side of the lesion in the temporal lobe. Neither the original authors nor Dr. Anthony considers this sign to be conclusively diagnostic, but at the same time this work represents a decided step forward in the complicated business of interpreting labyrinthine responses.

It is only by continued interest and work that major steps forward are made in physiology and medicine. All the stumbling blocks will not be overcome in a short period, and all the answers in vestibular physiology will not be discovered by one man. But the conjoined efforts of all those interested in otology and neurology ultimately will result, I feel sure, in a better understanding of this complex mechanism. If each decade in modern medical history offers even one more such significant step forward as the work of the London group, or its confirmation by Dr. Anthony, medical progress in our time shall not have been neglected.

CASE REPORTS

ACUTE LUPUS ERYTHEMATOSUS
Treatment with Prolonged Administration of Cortisone Orally
A Case Report

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THE history of lupus as a systemic disease makes a fascinating chapter in medical history. Important contributions have been made by Kaposi,[9] Osler,[17] Libman and Sacks,[12] Klemperer, Pollack, and Baehr,[11] and Felty and Keefer.[10] More recent advances include recognition and methods of identification of the L. E. cell by Hargraves[4] and Haserick[6] in 1948 and still more recently the use of cortisone and ACTH in treatment of this disease.

According to Haserick,[5] the introduction of cortisone has revolutionized the treatment of disseminated lupus. It may well be, and observations made in the case here reported suggest, that the fatal course of this disease may be modified toward a more benign and latent form under the influence of prolonged continuous administration of cortisone given orally in small doses.

CASE REPORT

C. C., a 16 year old Latin-American girl, was previously always healthy. On July 25, 1951, when she was first seen as an office patient, a diagnosis was made of an untreated but healing exudative tonsillitis of two weeks' duration. On July 11 a white coat had been noted on each tonsil when she looked in a mirror.

When first seen, the patient had moderate swelling of the eyelids, face, legs, and hands. The tonsils were large but no longer coated. Blood pressure was 166/106. Urinalysis revealed a specific gravity of 1.003 with 3 plus albumin; 12 to 15 red blood cells per high powered field, 3 to 6 white blood cells per high powered field; and occasional granular casts. Temperature was 99.2 F. A tentative diagnosis of acute hemorrhagic glomerulonephritis was made. The patient was placed on a therapeutic regimen of bed rest at home, low-salt diet, and oral magnesium sulfate and ammonium chloride. Because the tonsils were large and red and the throat sore, she was given one injection of 800,000 units of repository penicillin.

An office progress note August 1 indicated that the patient had been staying at home in bed since first seen on July 25. She had gradually improved. Edema had cleared greatly within the first three days of bed rest, though slight edema persisted. Blood pressure gradually dropped to 140/96 on the third day of bed rest. A small output of rather dark urine, approximately 600 cc. for twenty-four hours, persisted. Moderately severe epistaxis occurred July 30. Two days after the epistaxis, the blood pressure was found to be normal, 120/80, and the urine output had increased to 2,200 cc. of clear amber urine for twenty-four hours.

The patient improved steadily, except for the persistently abnormal microscopic urinary findings. However, on August 26 she suddenly developed high fever; tachycardia; a severe generalized maculopapular rash over the entire body; a recurrence of severe sore throat; an enanthema in the mouth

resembling the exanthema; wheezing rales over both lungs; several small hemoptyses of bright blood; severe arthralgia; and a severe recrudescence of the previously improving nephritis.

She was hospitalized August 28 at the Santa Rosa Hospital, where physical examination revealed the following additional findings: temperature 102 F.; pulse 102; respiration 24; blood pressure 160/100. The patient appeared acutely and severely ill, extremely toxic and at times delirious, with a severe widespread confluent maculopapular rash over the entire body, closely resembling measles except that the conjunctivae and sclerae were clear. The entire face was puffy and swollen. A peculiar enanthema was noted over the entire buccal mucosa, consisting of small punctate discrete erythematous foci, some of which were confluent. Some of these foci appeared purpuric and did not blanch on pressure; there were also several purpuric areas on and about the lips as well as in scattered areas over the skin wherever the rash was most severe. This combination of purpura and erythema gave the rash a peculiar salmon-pink coloration. Scattered wheezing rales were heard over both lung fields. Over the mitral area the apex beat was visible and palpable but not displaced. A fairly loud systolic murmur was heard at the pulmonary area in the second left interspace, also along the left sternal border, and at the apex, where its intensity was much less. The pulmonic second sound was louder than the aortic second sound. (Whether the pulmonary and apical systolic murmurs represented a single bruit with transmission or whether two murmurs of separate origin were present could not be determined definitely on admission. Later in the hospital course, they appeared to be separate murmurs.) The abdomen was slightly distended but soft. There was 2 to 3 plus pitting edema over the legs up to the knees. The small joints of the fingers and toes were reddened and extremely tender, also painful both at rest and on motion. Neuropsychiatric examination was notable for delirium, mainly nocturnal, and for generalized slight hyperreflexia of the tendon reflexes.

Admission Laboratory Data.—A blood Wassermann test was negative. Hemoglobin was 71 per cent (Haden-Hauser); red blood cells numbered 3,300,000, white blood cells 4,600; nonprotein nitrogen was 45 mg. per 100 cc.; sedimentation rate 99 mm. per hour (Westergren); serum albumin 2.9 Gm. per 100 cc.; serum globulin 4.1 Gm. per 100 cc.; serum calcium 7.9 mg. per 100 cc.; serum phosphorus 3.4 mg. per 100 cc.; blood chlorides were 507 mg. per 100 cc.; platelet count was normal; capillary fragility test (arm tourniquet) strongly positive. Urinalysis revealed a specific gravity of 1.000; albumin 3 plus; red and white blood cells 20 to 30 per high powered field; casts 5 to 10 per high powered field.

Course in Hospital.—On August 29 administration orally of cortisone, 100 mg. twice daily, was begun; this was continued throughout the patient's hospital course until decrease of dosage on September 2 to 25 mg. thrice daily. Fluids were not restricted and a high protein, low-sodium diet was given. There was a rapid improvement of all symptoms and signs on this regimen. Temperature and pulse, which had spiked as high as 104 F. and 130 respectively on August 28, had returned to normal by August 30, and temperature and pulse remained normal after this date. The rash steadily faded, and by the time of the patient's discharge September 5, showed only a general residual moderate pigmentation. Joint signs and symptoms disappeared completely within four days. Edema had cleared within seventy-two hours. There was a forceful and palpable point of apical maximal impulse, not displaced, and a rather loud systolic apical murmur noted on the day of discharge. Leukopenia cleared within three days and nonprotein nitrogen in the blood was normal on discharge. Sedimentation rate remained rapid, 78 mm. per hour on September 3. Moderate anemia noted on admission was still present on discharge. There was marked improvement in the urinary findings: on the day of discharge the microscopic sediment showed only a few epithelial cells and there was no albuminuria. Blood pressure was 138/84 on discharge.

Management on Cortisone Therapy.—Following discharge of the patient from the hospital, it was decided to decrease the dosage of cortisone to a minimum that would prevent overdosage but still maintain the patient free of acute lupus crises or minor exacerbations. The decision to try continuous rather than intermittent dosage was based largely on Baehr's findings.[14] Baehr stated in summary: "Exacerbations that follow attempts to discontinue therapy indicate that long range or even permanent treatment may be necessary to control this disease."

The patient remained at home on a bed rest regimen, with the shades drawn. Cortisone administration was maintained at 25 mg. twice daily for one week, then 25 mg. daily for two weeks. By September 24, the patient's general condition had improved remarkably. She was afebrile, the rash was entirely gone, her appetite was good, there were no joint symptoms, systolic blows at pulmonic and mitral areas were of only moderate intensity, and laboratory findings were normal (fig. 1). Blood pressure was 138/84. Discontinuance of therapy for three days at this point was followed promptly by a recurrence of swelling of the eyelids, fever, decreased urinary output, albuminuria, and numerous red cells, casts, and white cells in the previously clear urinary sediment; the fairly loud murmur over the pulmonic and mitral areas was unchanged; and an electrocardiogram at this time showed only a main axis deviation of plus 80 degrees. Renewal of cortisone therapy at 12.5 mg. twice daily was followed by a prolonged period of well-being with disappearance of the fever, an average urinary output of 2,500 cc. daily, and an asymptomatic course throughout October.

On November 30, in an attempt to clear the recurrent urinary findings, cortisone was increased from 12.5 mg. twice daily to 12.5 mg. thrice daily. On December 3, there was noted for the first time a slightly more circular contour of the face and a growth of forearm hair slightly heavier than normal. These two slight signs have persisted unchanged up to the present time and no other signs suggesting overactivity of the adrenal cortex have appeared.

However, in an attempt to rid the patient of these two slight signs, cortisone was decreased to 12.5 mg. twice daily. This attempt at perfectionism coincided with the patient's decision to test her newly-recovered sense of well-being by taking a long walk in the bright San Antonio sunshine, without a hat. On December 7, the day following the walk in the sun, signs of a severe lupus relapse and incipient crisis appeared: slight fever, tachycardia, and a recurrence of the diffuse salmon-pink erythematous rash over the cheeks, bridge of nose, upper anterior chest, and dorsal surfaces of the forearms, arms, and legs. The patient's chief complaint was that her hands "burned"; the finger pads became tender, and there were some points of tenderness on the phalangeal joints. A consultant dermatologist on December 11 stated that the rash was typical of lupus erythematosus, especially on the face, but that the floridity of the rash was being fairly well inhibited by the small oral maintenance dose of cortisone. On increased dosage (fig. 1) the rash had almost completely subsided within five days, with simultaneous clearing of all the other symptoms and signs.

Following recovery from this relapse, the patient's course has been happily uneventful. On January 18, 1952, 10 cc. of

the patient's whole blood was drawn and sent to Dr. Haserick in Cleveland for his plasma L. E. test. This was reported as negative. It is known that L. E. cells may not always be found during ACTH-induced remissions,[16] but exact statistics on this point for cortisone-maintained remissions in large series of cases have not as yet accumulated in the literature. In Baehr's series,[14] L. E. cells persisted in 13 of 14 patients in remissions. Most of his remissions, however, were maintained only intermittently with relatively large parenteral doses of ACTH rather than with prolonged continuous small oral dosage of cortisone, as in my case. Brunsting,[1] discussing the L. E. test, concluded that "a negative result of a test does not exclude the presence of the disease in a milder form or in remission."

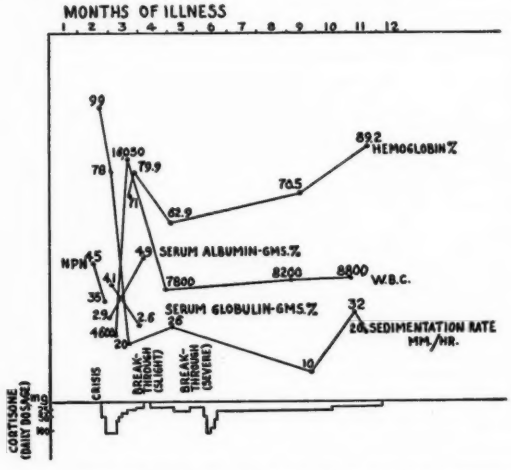

FIG. 1. Graph showing the correlation of clinical and laboratory data with daily cortisone dosage in a case of lupus erythematosus.

Cortisone has now been given continuously in the present case for the past nine months, with decrease in the oral dosage to 5 mg. thrice daily during the past two months (fig. 1). On March 20, 1952, the patient returned to her former work as a typist. She is now being seen about twice monthly, and her general condition is excellent.

DISCUSSION

Certain questions and problems present themselves in any study of cortisone maintenance in disseminate lupus. These problems simply will be outlined, inasmuch as any definite answers to them must await the passage of time and the accumulation of large series of cases.

Underactivity of Adrenal Cortex.—Atrophy of the adrenal glands has been reported in patients with severe lupus who became progressively worse and died despite large doses of cortisone.[1] This would not necessarily mean a similar finding in cases such as the one here reported, in which much smaller dosage has maintained remission for months, and may possibly continue to do so even for years.

Overactivity of Adrenal Cortex.—Frequent evidence of severe overactivity of the adrenal cortex has been reported in prolonged cortisone treatment. Soffer, Levitt, and Baehr[14] reported many untoward effects, including hypertension, edema, depression, increased pigmentation, hirsutism, convulsions, congestive heart failure, permanent diabetes mellitus, and transient auricular fibrillation. These authors stated their maintenance dosage in only 1 case, at least 50 to 75 mg. daily, but many of their intermittent dosages were larger, such as 100 to 150 mg. daily for seventy-five days in 1 case. The present case study suggests that smaller maintenance doses of cortisone in lupus erythematosus may result in fewer and milder complications.

Discontinuance of Cortisone.—In the studies reported thus far it would appear that in the majority of cases cortisone cannot be safely discontinued in acute lupus remissions. Soffer, Levitt, and Baehr[14] reported that of 6 patients treated and remissions induced, it was subsequently possible to discontinue therapy in only 1. In this 1 case a relapse occurred after treatment was discontinued for a three-month period; the relapse responded promptly to ACTH. In 2 patients an attempt was made to maintain the cortisone remission by injections on alternate days; clinical manifestations recurred in both cases. Maintenance dosage was reported as reduced in 2 cases, but the minimal maintenance dosage reported in their series was 50 to 75 mg. daily.

Cost.—The high cost of prolonged or "permanent" cortisone administration has been an important, at times a crucial, consideration. The lessened cost of smaller dosage is another consideration in further trial of this plan of treatment in lupus.

Cortisone or ACTH.—The decision to treat this patient with cortisone rather than ACTH was based largely on the reports of Irons[7] and his associates. These reports indicated that in the severe acute phase ACTH appeared to have induced more rapid remissions; but because of the reported higher incidence and greater severity of complications when ACTH was used for long-term therapy, it appeared that cortisone would be more suitable for maintenance in this patient. Also, by using cortisone for the lupus crisis as well as for maintenance, there was no need for the change-over from ACTH to cortisone. Finally cortisone could be taken orally, which made it much more suitable for long-term management than the injectable ACTH.

Control of Basic Disease.—Another question presented itself in this case and constantly faces any physician whose lupus patient is in remission on cortisone: Is the disease under adequate control? This is not always easy to answer, especially since the basic disease process itself is still to a large extent unknown.

The absence of fever and tachycardia, complete disappearance of the loud heart murmur, normal or only slightly elevated blood pressure, minimal findings on weekly urinalyses, continued appearance and feeling of well-being, mild rather than severe anemia, normal white blood cell count, and ability to return to work are all considered as points of evidence that the basic lupus process has been under adequate control in my patient for nine months. An extremely valuable guide as to activity or quiescence of the L. E. process proved to be the sedimentation rate,[5] as indicated in figure 1. In this case, the albumin-globulin ratio also has paralleled the clinical course, as indicated. Boas and Soffer[14] have emphasized the serum glucosamine values as good laboratory indicators of the clinical course.

Differential Diagnosis.—During cortisone administration, certain isolated symptoms and signs appeared sporadically, about which one could wonder whether they came from the protean primary disease or from a similarly protean clinical picture of excessive cortisone. These similar signs have included in the present patient, at various times, transient edema of the eyelids, face, and lower legs; transient elevations of blood pressure; slight tendon hyperreflexia; and slight emotional instabilities. A general clinical appraisal was the deciding factor here, but the normality or abnormality of the sedimentation rate was helpful in deciding whether an early cortisone overdosage or an early lupus relapse was present.

Residuals.—It is apparent that certain lupus manifestations tend to persist despite therapy with cortisone. In this case the cardiac murmurs persisted until the fifth month on cortisone therapy. They have not recurred to date. Urinary findings indicative of nephritis have persisted; these findings are usually slight, but occasionally severe with showers of casts and red cells. Blood pressure, which was definitely elevated during the acute phase, has fluctuated between normal tension and slight elevation. A residual moderate hypochromic anemia persisted until the eighth month of cortisone (fig. 1). Soffer in 14 cases listed persistent renal abnormalities in 5; anemia in 14; L. E. cells in 14; leukopenia in 10; and thrombocytopenia in 7.[13]

Single Course Versus Intermittent Dosage.—The question of continuous or intermittent therapy is still under debate in the literature. Johnson and Meyer[8] concluded: "It is our impression that the interrupted schedule which we employed is somewhat more satisfactory than the continuous therapy of large doses, 100 to 200 mgm. daily for a total of 6 gm. Tapering of the dosage and still more prolonged therapy may be wiser still."

Size of Dose.—It is noteworthy that this patient has been maintained on what might be considered an unusually small dosage of cortisone. However, Paulsen,[13] working with ACTH, calculated the daily maintenance dose at 25 mg. daily, divided into four doses of 6.25 mg. each; he used the eosinopenic index as his basis of calculation. He expressed the belief that the daily adrenal steroid doses of 100 to 200 mg. used widely in America are unphysiologic. Thompson,[15] reviewing Paulsen's work, stated: "Paulsen's opinion that the dose of ACTH given by most American workers is too large will probably be proved correct in many instances as extended studies with smaller doses are reported." Conn[3] has stated the belief that cortisone maintenance doses of 100 mg. or more in current use are "astronomically high" and he pointed out that 5 mg. of cortisone daily will maintain a patient with Addison's disease in complete health.

A comment should certainly be made on the general ambulatory or office care of the lupus remission. Generally the patient reported upon here feels so good—possibly as a nonspecific psychic effect of the cortisone—that it is sometimes difficult to persuade her that she needs a doctor at all. However, since her second exacerbation, she is willing to listen to periodic re-cautionings as to avoidance of (1) strong sunlight, (2) prolonged strenuous physical exertion, (3) extremes of heat or cold, (4) sudden changes in body temperature, (5) upper and lower respiratory infections and any foci of infection, and (6) any known or suspected allergens.

The disseminated lupus patient in cortisone-maintained remission constitutes a new clinical status, and may perhaps be compared to the status of the patient with severe diabetes shortly after the introduction of insulin. He (or more often she) is beginning to live validly rather than invalidly and probably beyond the previously allotted time. How far these remissions can be extended, and the proper means of control of these patients and their formerly uniformly highly fatal disease, must remain a subject for further study.

CONCLUSIONS

Introduction of cortisone has given a new and more hopeful clinical status to the patient with disseminated lupus erythematosus.

A case is reported in which an attempt is made to manage this disease by means of prolonged continuous small oral dosage of cortisone. Thus far, for nine months, this plan of management has been satisfactory.

Various new and still undecided questions and problems concerning the management of disseminated lupus erythematosus are outlined and discussed briefly.

ADDENDUM

In August, 1952, the patient discontinued cortisone of her own volition, mainly because of the expense and the fact that she felt well, and despite my advice to continue medications; she exhibited no symptoms or signs of underactivity of the adrenal cortex at any time and has continued well and working without cortisone. Periodic examinations to date are negative except for some abnormal urinary findings (slight albuminuria, occasional red blood cells, rare casts) which have almost disappeared recently. Blood pressure is normal.

REFERENCES

1. Brunsting, L. A.: Acute Disseminated Lupus Erythematosus, M. Clin. North America (March) 1951, pp. 399-409.
2. Brunsting, L. A.; Slocumb, C. H.; and Didcoct, J. W.: Effects of Cortisone on Acute Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. *25*:479-482 (Aug. 16) 1950; Arch. Dermat. & Syph. *63*:29-52 (Jan.) 1951.
3. Conn, J.: Quoted by Lamb, J. H.; Young, C. J.; and Keatz, C.: Therapy of Chronic and Acute Lupus Erythematosus, Postgrad. Med. *10*:182-186 (Sept.) 1951.
4. Hargraves, M. M.; Richmond, H.; and Morton, R.: Presentation of Two Bone Marrow Elements: "Tart" Cell and "L. E." Cell, Proc. Staff Meet., Mayo Clin. *23*:25-28 (Jan. 21) 1948.
5. Haserick, J. R., in Conn, H. F.: Current Therapy, Philadelphia, W. B. Saunders Co., 1952.
6. Haserick, J. R., and Bortz, D. W.: New Diagnostic Test for Acute Disseminated Lupus Erythematosus, Cleveland Clin. Quart. *16*: 158-161 (July) 1949.
7. Irons, E. N.; Ayer, J. P.; Brown, R. G.; and Armstrong, S. H., Jr.: ACTH and Cortisone in Diffuse Collagen Disease and Chronic Dermatoses, J.A.M.A. *145*:861-869 (March 24) 1951.
8. Johnson, S. A. M., and Meyer, O. O.: Treatment of Lupus Erythematosus Disseminatus with Cortisone, Am. J. M. Sc. *223*:9-15 (Jan.) 1952.
9. Kaposi, M.: Neue Beiträge zur Kentniss des Lupus Erythematosus, Arch. f. Dermat. u. Syph. *4*:36-78, 1872.
10. Keefer, C. S., and Felty, A. R.: Acute Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. *35*:294-304 (Sept.) 1924.
11. Klemperer, P.; Pollack, A. D.; and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. *32*:569-631 (Oct.) 1941.
12. Libman, E., and Sacks, B.: Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. *33*:701-737 (June) 1924.
13. Paulsen, F.: Pharmacological and Clinical Results with ACTH in 112 Cases, Acta Endocrinol. *5*:292-326, 1950.
14. Soffer, L. J.; Levitt, M. F.; and Baehr, G.: Use of Cortisone and Adrenocorticotropic Hormone in Acute Disseminated Lupus Erythematosus, Arch. Int. Med. *86*:558-573 (Oct.) 1950.
15. Thompson, W. O.: Year Book of Endocrinology, Chicago, Year Book Publishers, 1950, p. 54.
16. Thorn, G. W., and others: Clinical Usefulness of ACTH and Cortisone, New England J. Med. *242*:824-834 (May 25) 1950.
17. Tumulty, P. A., and Harvey, A. M.: Clinical Course of Disseminated Lupus Erythematosus; Evaluation of Osler's Contributions, Bull. Johns Hopkins Hosp. *85*:47-73 (July) 1949.

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NEWS

COMING MEETINGS AND CLINICS

Texas Medical Association, San Antonio, May 3-5, 1954. Dr. George Turner, El Paso, Pres.; Mr. N. C. Forrester, 1801 Lamar Blvd., Austin, Executive Secy.

American Medical Association, St. Louis, Dec. 1-4, 1953. Dr. Edward J. McCormick, Toledo, Ohio, Pres.; Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secy.

NATIONAL AND REGIONAL

American Academy of Allergy, Houston, Feb. 1-3, 1954. Dr. Ben Z. Rappaport, Chicago, Pres.; Dr. Alan G. Cazort, 1425 West 7th St., Little Rock, Secy.

American Academy of Dermatology and Syphilology, Chicago, Dec. 5-10, 1953. Dr. Michael H. Ebert, Chicago, Pres.; Dr. John E. Rauschkolb, 25 Prospect Ave., N W., Cleveland 15, Secy.

American Academy of General Practice. Dr. R. B. Robins, Camden, Ark., Pres.; Mr. Mac F. Cahal, 406 W. 34th St., Kansas City 2, Executive Secy.

American Academy of Obstetrics and Gynecology, Cincinnati, Dec. 14-16, 1953. Dr. Robert A. Kimbrough, Jr., Philadelphia, Pres.; Dr. C. Paul Hodgkinson, Detroit, Secy.

American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 12-16, 1953. Dr. Frederick C. Cordes, San Francisco, Pres.; Dr. W. L. Benedict, 100 First Ave. Bldg., Rochester, Minn., Secy.

American Academy of Pediatrics, Miami, Oct. 6-9, 1953. Dr. Phillip Barba, Philadelphia, Pres.; Dr. E. H. Christopherson, 610 Church St., Evanston, Ill., Secy.

American Association for Thoracic Surgery, Montreal, Canada, May 3-5, 1954. Dr. Emile F. Holman, San Francisco, Pres.; Dr. Paul C. Samson, 2938 McClure St., Oakland 9, Calif., Secy.

American Association of Genito-Urinary Surgeons, Shawnee-on Delaware, Pa., May 26-28, 1954. Dr. Vincent J. O'Conor, Chicago, Pres.; Dr. Norris J. Heckel, 122 S. Michigan Ave., Chicago 3, Secy.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10-12, 1953. Dr. Nicholson J. Eastman, Baltimore, Pres.; Dr. William F. Mengert, 2211 Oak Lawn Ave., Dallas, Secy.

American Cancer Society. Dr. Guy Aud, Louisville, Ky., Pres.; Mr. M. R. Runyon, 47 Beaver St., New York, Executive Vice-Pres.

American College of Allergists, Miami Beach, April 5-10, 1954. Dr. M. Murray Peshkin, New York, Pres.; Dr. Fred W. Wittich, 423 La Salle Medical Bldg., Minneapolis 2, Secy.

American College of Chest Physicians, San Francisco, June 17-20, 1954. Dr. Alvis E. Greer, Houston, Pres.; Mr. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Executive Secy.

American College of Physicians, Chicago, April 5-9, 1954. Dr. Leroy H. Sloan, Chicago, Pres.; Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Secy.

American College of Radiology, Chicago, February, 1954. Dr. John D. Camp, Los Angeles, Pres.; Mr. W. C. Stronach, 20 N. Wacker Drive, Chicago 6, Executive Secy.

American College of Surgeons, Chicago, Oct. 5-9, 1953. Dr. Harold L. Foss, Danville, Pa., Pres.; Dr. Michael L. Mason, 40 E. Erie St., Chicago 11, Secy.

American Congress of Physical Medicine and Rehabilitation, Chicago, Aug. 31-Sept. 4, 1953. Dr. Walter M. Solomon, Cleveland, Pres.; Dr. Frances Baker, 1 Tilton Ave., San Mateo, Calif., Secy.

American Dermatological Association, White Sulphur Springs, W. Va., April 13-17, 1954. Dr. Louis A. Brunsting, Rochester, Minn., Pres.; Dr. J. Lamar Callaway, Duke Hospital, Durham, N. C., Secy.

American Gastro-Enterological Association, San Francisco, June 18-19, 1954. Dr. J. M. Ruffin, Durham, N. C., Pres.; Dr. H. Marvin Pollard, 1313 E. Ann St., Ann Arbor, Mich., Secy.

American Gynecological Society, Hot Springs, Va., May 20-22, 1954. Dr. Richard W. TeLinde, Baltimore, Pres.; Dr. John I. Brewer, 104 S. Michigan Ave., Chicago, Secy.

American Hospital Association, San Francisco, Aug. 31-Sept. 3, 1953. Dr. Edwin L. Crosby, Chicago, Pres.; Mr. George P. Bugbee, 18 E. Division St., Chicago, Executive Secy.

American Laryngological, Rhinological, and Otological Society, Boston, May 25-27, 1954. Dr. LeRoy A. Schall, Boston, Pres.; Dr. C. S. Nash, 277 Alexander St., Rochester 7, N. Y., Secy.

American Neurological Association, Atlantic City, N. J., June 14-16, 1954. Dr. Roland P. Mackay, Chicago, Pres.; Dr. H. Houston Merritt, 710 W. 168th St., New York 32, Secy.

American Ophthalmological Society, Glacier Park, Mont., June 16-18, 1954. Dr. William L. Benedict, Rochester, Minn., Pres.; Dr. M. C. Wheeler, 30 W. 59th St., New York 19, Secy.

American Orthopedic Association, Bretton Woods, N. H., June 6-9, 1954. Dr. A. R. Shands, Jr., Wilmington, Del., Pres.; Dr. George O. Eaton, 4 E. Madison St., Baltimore 2, Secy.

American Pediatric Society, Buck Hill Falls, Pa., May 3-5, 1954. Dr. Rustin McIntosh, New York, Pres.; Dr. Aims McGuinness, 237 Medical Laboratory, University of Pennsylvania, Philadelphia 46, Secy.

American Proctologic Society, Los Angeles, June 2-5, 1954. Dr. Wendall Green, Toledo, Ohio, Pres.; Dr. Stuart T. Ross, 131 Fulton Ave., Hempstead, N. Y., Secy.

American Psychiatric Association, St. Louis, May 3-7, 1954. Dr. Kenneth E. Appel, Philadelphia, Pres.; Dr. R. Finley Gayle, 6300 Three Chopt Rd., Richmond 21, Va., Secy.

American Public Health Association, New York, Nov. 9-13, 1953. Dr. Wilton L. Halverson, San Francisco, Pres.; Dr. R. W. Atwater, 1790 Broadway, New York 19, Executive Secy.

American Society of Anesthesiologists, Seattle, Oct. 6-9, 1953. Dr. Ralph T. Knight, Minneapolis, Pres.; Dr. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago, Secy.

American Society of Clinical Pathologists, Chicago, Oct. 12-16, 1953. Dr. Henry F. Hunt, Danville, Pa., Pres.; Dr. Clyde G. Culbertson, Indiana University School of Medicine, Indianapolis, Secy.

American Surgical Association, Cleveland, April, 1954. Dr. Howard C. Naffziger, San Francisco, Pres.; Dr. R. Kennedy Gilchrist, 59 East Madison St., Chicago, Secy.

American Urological Association, New York, May 31-June 3, 1954. Dr. J. A. Campbell Colston, Baltimore, Md., Pres.; Dr. C. H. DeT. Shivers, 121 S. Illinois Ave., Atlantic City, N. J., Secy.

Association of American Physicians and Surgeons, Chicago, Oct. 8-10, 1953. Dr. Charles L. Farrell, Pawtucket, R. I., Pres.; Mr. Harry E. Northam, 360 N. Michigan Ave., Chicago 1, Executive Secy.

International College of Surgeons, U. S. Chapter, New York, Sept. 14-18, 1953. Dr. William R. Lovelace, Albuquerque, N. M., Pres.; Dr. Karl Meyer, 1516 Lake Shore Drive, Chicago, Secy.

National Tuberculosis Association, Atlantic City, N. J., May 17-21, 1954. Mr. Mark H. Harrington, Denver, Pres.; Mr. Kemp D. Battle, 1790 Broadway, New York 19, Secy.

Radiological Society of North America, Chicago, Dec. 13-18, 1953. Dr. Ira H. Lockwood, Kansas City, Mo., Pres.; Dr. D. S. Childs, 713 E. Genesee, Syracuse 2, N. Y., Secy.

Southern Medical Association, Atlanta, Ga., Oct. 26-29, 1953. Dr. Walter C. Jones, Miami, Pres.; Mr. C. P. Loranz, 1020 Empire Bldg., Birmingham 3, Ala., Secy.

Southern Psychiatric Association, Biloxi, Miss., Oct. 4-6, 1953. Dr. R. Burke Suitt, Durham, N. C., Pres.; Dr. Joseph L. Knapp, 210 N. Westmoreland, Dallas, Secy.

Southern Surgical Association, Hot Springs, Va., Dec. 8-10, 1953. Dr. I. A. Bigger, Richmond, Va., Pres.; Dr. John C. Burch, 2112 West End Ave., Nashville 5, Tenn., Secy.

Southwest Allergy Forum. Dr. Orval R. Withers, Kansas City, Mo., Pres.; Dr. Frederic Speer, 2601 Parallel Ave., Kansas City 4, Mo., Secy.

Southwest Regional Cancer Conference, Fort Worth, Sept. 23-24, 1953. Secy., 209 Medical Arts Bldg., Fort Worth.

Southwestern Medical Association, Tucson, Oct. 29-31, 1953. Dr. Wesley O. Connor, Jr., Albuquerque, N. M., Pres.; Dr. Celso Stapp, 800 Montana, El Paso, Secy.

Southwestern Surgical Congress, Salt Lake City, Utah, Sept. 21-23, 1953. Dr. Louis P. Good, Texarkana, Ark., Pres.; Dr. C. R. Rountree, 1227 Classen, Oklahoma City 3, Secy.

Tri-State Medical Assembly. Dr. Frank G. Thibault, El Dorado, Ark., Pres.; Dr. Albert M. Hand, Le Bonheur Children's Hospital, Memphis 3, Tenn., Secy.

United States-Mexico Border Public Health Association, Albuquerque, N. M., April, 1954. Mr. Richard F. Poston, Dallas, Pres.; Dr. Sidney B. Clark, 314 U. S. Court House, El Paso, Secy.

STATE

Private Clinics and Hospitals Association of Texas, Austin, Dec. 5-6, 1953. Dr. S. D. Coleman, Navasota, Pres.; Dr. Neil D. Buie, Marlin, Secy.

Texas Academy of General Practice, Dallas, Sept. 21-23, 1953. Dr. C. U. Callan, Rotan, Pres.; Dr. Woodson W. Harris, 1410 Nickerson, Austin, Secy.

Texas Academy of Internal Medicine, Houston, December, 1953. Dr. Hatch W. Cummings, Jr., Houston, Pres.; Dr. George M. Jones, 1314 Medical Arts Bldg., Dallas, Secy. Meetings restricted to members.

Texas Air-Medics Association, San Antonio, May, 1954. Dr. George L. Gallaher, Harlingen, Pres.; Dr. J. S. Minnett, 2512 Welborn, Dallas, Secy.

Texas Association of Blood Banks, Fort Worth, Dec. 4-5, 1953. Dr. W. N. Powell, Temple, Pres.; Miss Majorie Saunders, 3500 Gaston Ave., Dallas, Secy.

Texas Association of Obstetricians and Gynecologists, Waco, Feb. 19-20, 1954. Dr. D. D. Wall, San Angelo, Pres.; Dr. Carey Hiett, 815 Fifth Ave., Fort Worth, Secy.

Texas Chapter, American College of Chest Physicians, San Antonio, May 2, 1954. Dr. Henry H. Hoskins, San Antonio, Pres.; Dr. Walter C. Brown, 1733 S. Brownlee Blvd., Corpus Christi, Secy.

Texas Club of Internists. Dr. Joseph F. McVeigh, Fort Worth, Pres.; Dr. Charles Darnall, Capital National Bank Bldg., Austin, Secy.

Texas Dermatological Society, San Antonio, May 2, 1954. Dr. Maurice Barnes, Waco, Pres.; Dr. Thomas L. Shields, 1216 Pennsylvania Ave., Fort Worth, Secy.

Texas Diabetes Association, San Antonio, May 2, 1954. Dr. Raymond L. Gregory, Galveston, Pres.; Dr. Edmond K. Doak, 501 Hermann Professional Bldg., Houston, Secy.

Texas Division, American Cancer Society. Mr. Travis Wallace, Dallas, Pres.; Mr. J. Louis Neff, 1609 Colorado, Austin, Executive Director.

Texas Heart Association, San Antonio, May 3, 1954. Dr. Joseph McVeigh, Fort Worth, Pres.; Miss Roberta Miller, 412 Fidelity Union Life Bldg., 1511 Bryan St., Dallas, Executive Secy.

Texas Hospital Association, Houston, May 18-20, 1954. Mr. W. U. Paul, El Paso, Pres.; Mrs. Ruth Barnhart, 2210 Main St., Dallas, Secy.

Texas Neuropsychiatric Association, San Antonio, May 2, 1954. Dr. James Blair, San Antonio, Pres.; Dr. John L. Otto, John Sealy Hospital, Galveston, Secy.

Texas Orthopedic Association, San Antonio, May 3, 1954. Dr. Edward T. Smith, Houston, Pres.; Dr. Margaret Watkins, 3629 Fairmount St., Dallas, Secy.

Texas Pediatric Society, Corpus Christi, Oct. 2-3, 1953. Dr. J. A. Bybee, Beaumont, Pres.; Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Secy.

Texas Public Health Association, Galveston, Feb. 14-17, 1954. Dr. Roy G. Reed, La Marque, Pres.; Mr. Earle W. Sudderth, Dallas County Health Department, Court House, Dallas, Executive Secy.

Texas Radiological Society, Dallas, Jan. 29-30, 1954. Dr. J. E. Miller, Dallas, Pres.; Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth, Secy.

Texas Railway and Traumatic Surgical Association, San Antonio, May 3, 1954. Dr. William E. Crump, Wichita Falls, Pres.; Dr. W. D. Marrs, 306 Broadway, Fort Worth, Secy.

Texas Rheumatism Association, Houston, Dec. 4, 1953. Dr. J. C. Crager, Beaumont, Pres.; Dr. Charles H. Cornwell, Marlin, Secy.

Texas Society for Mental Health, Waco, March 4-6, 1954. Mrs. Frank Schoonover, Fort Worth, Pres.; Mrs. Elizabeth F. Gardner, 2504 Jarratt Ave., Austin 21, Executive Secy.

Texas Society of Anesthesiologists, San Antonio, May 2, 1954. Dr. James B. Robinett, Jr., Houston, Pres.; Dr. C. R. Allen, John Sealy Hospital, Galveston, Secy.

Texas Society of Gastroenterologists and Proctologists, San Antonio, May, 1954. Dr. Cecil O. Patterson, Dallas, Pres.; Dr. W. T. Arnold, 1402 Hermann Prof. Bldg., Houston, Secy.

Texas Society of Ophthalmology and Otolaryngology, Fort Worth, Dec. 4-5, 1953. Dr. Dan Brannin, Dallas, Pres.; Dr. Lyle Hooker, 627 Esperson Bldg., Houston, Secy.

Texas Society of Pathologists, Galveston, Jan. 31, 1954. Dr. A. O. Severance, San Antonio, Pres.; Dr. Lloyd R. Hershberger, Shannon Memorial Hospital, San Angelo, Secy.

Texas Surgical Society, Dallas, Oct. 5-6, 1953. Dr. George W. Waldron, Houston, Pres.; Dr. Albert W. Hartman, 414 Navarro St., San Antonio 5, Secy.

Texas Tuberculosis Association, Dallas, April 9-10, 1954. Dr. R. G. McCorkle, San Antonio, Pres.; Miss Pansy Nichols, 208 E. Ninth, Austin, Executive Secy.

Texas Urological Society. Dr. R. E. Cone, Galveston, Pres.; Dr. Ray M. Morgan, Jr., Hermann Hospital, Houston, Secy.

DISTRICT

First District Society, Pecos, February, 1954. Dr. John W. O'Donnell, Alpine, Pres.; Dr. H. D. Garrett, First National Bldg., El Paso, Secy.

Second District Society, Sweetwater, April 15, 1954. Dr. T. D. Young, Sweetwater, Pres.; Dr. Francis Hood, Sweetwater, Secy.

Third District Society, Amarillo, April 13, 1954. Dr. Robert A. Neblett, Canyon, Pres.; Dr. James T. Hall, 1626 Fifteenth St., Lubbock, Secy.

Fourth District Society, Brownwood, Oct. 8, 1953. Dr. Lloyd R. Hershberger, San Angelo, Pres.; Dr. Paul M. Wheelis, Brownwood, Secy.

Fifth and Sixth Districts Society, Corpus Christi, July, 1954. Dr. Y. C. Smith, Sr., Corpus Christi, Pres.; Dr. Robert J. Sigler, 1126 Third Street, Corpus Christi, Secy.

Seventh District Society, Austin, Feb. 18, 1954. Dr. Benjamin Clary Bates, Austin, Pres.; Dr. William McLean, 4618 Burnet Road, Austin, Secy.

Eighth District Society, Wharton, Oct. 8, 1953. Dr. Andrew S. Tomb, Victoria, Pres.; Dr. George E. Glover, Jr., Victoria, Secy.

Ninth District Society, Brenham, March 25, 1954. Dr. George D. Bruce, Baytown, Pres.; Dr. Lyman C. Blair, 1212 Rothwell, Houston, Secy.

Tenth District Medical Society, Port Arthur, Oct. 3, 1953. Dr. Edmund D. Jones, Beaumont, Pres.; Dr. O. W. Harris, Jr., Liberty, Secy.

Eleventh District Society, Tyler, Fall, 1953. Dr. Melvin R. Wilcox, Athens, Pres.; Dr. Marlin T. Braswell, Henderson, Secy.

Twelfth District Society, Waco, January, 1954. Dr. Howard Dudgeon, Jr., Waco, Pres.; Dr. Walter B. King, Jr., Waco, Secy.
Thirteenth District Society, Fort Worth, 1954. Dr. William E. Crump, Wichita Falls, Pres.; Dr. Robert D. Moreton, 815 Medical Arts Bldg., Fort Worth, Secy.
Fourteenth District Society, Denton, 1954. Dr. J. W. Atchison, Gainesville, Pres.; Dr. L. W. Johnston, 502 W. College St., Terrell, Secy.
Fifteenth District Society, Longview, April 20, 1954. Dr. L. E. Rutledge, Daingerfield, Pres.; Dr. George Tate, Longview, Secy.

CLINICS

Dallas Southern Clinical Society, Dallas, March 15-18, 1954. Miss Helga Boyd, Medical Arts Bldg., Dallas 1, Executive Secy.
Central Texas Spring Clinic, Waco, April 7, 1954. Dr. Walter B. King, 2320 Columbus Ave., Waco, Secy.
International Medical Assembly of Southwest Texas. Dr. John M. Smith, Jr., 205 Camden St., San Antonio, Secy.
New Orleans Graduate Medical Assembly, New Orleans, March 8-11, 1954. Dr. Maurice E. St. Martin, Room 103, 1430 Tulane Ave., New Orleans 12, Secy.
North Texas-Southern Oklahoma Fall Clinical Conference, Wichita Falls, Sept. 16, 1953. Dr. C. H. Wilson, Wichita Falls, Chairman.
Oklahoma City Clinical Society Conference, Oklahoma City, Oct. 26-29, 1953. Miss Alma F. O'Donnell, 512 Medical Arts Bldg., Oklahoma City 2, Executive Secy.
Postgraduate Medical Assembly of South Texas, 1954. Dr. Edward T. Smith, 906 Hermann Professional Bldg., Houston, Secy.
State Tumor Clinic. Dr. Bailey R. Collins, 925½ Scott Street, Wichita Falls, Director.

BOARD EXAMINATIONS

Texas State Board of Examiners in Basic Sciences, Austin, Oct. 16-17, 1953. Mrs. Betty Ratcliff, 407 Perry-Brooks Bldg., Austin, Chief Clerk.
Texas State Board of Medical Examiners, Fort Worth, Nov. 12-14, 1953. Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth, Secy.

1954 AAPS ESSAY CONTEST

Announcements of the 1954 essay contest for high school students conducted annually by the Association of American Physicians and Surgeons have been mailed to each county medical society and county auxiliary president in Texas by Dr. Mal Rumph of Fort Worth, national essay committee chairman.

The contest again will be sponsored on the state level by the Texas Medical Association and its Woman's Auxiliary. Drs. Charles D. Reece and Hampton C. Robinson, both of Houston, are members of the national committee. Mrs. A. O. Severance of San Antonio is state chairman of the Auxiliary committee.

As in the past, the subject of the contest will be, "Why the Private Practice of Medicine Furnishes This Country with the Finest Medical Care."

In the 1953 contest, second and third place national awards went to two Texas high school students. Approximately 55 per cent of the Texas county auxliaries participated in the contest, according to Dr. Rumph, who also stated that Districts 1, 2, 4, and 11 were 100 per cent in participation. He stressed the importance of each county medical society cooperating with its county auxiliary to carry on the contest locally. Fourteen state medical associations and county medical societies in twenty-seven other states took part in last year's competition.

Rules for the 1954 contest are as follows:

1. Junior and senior high school students, except children of physicians, from all public and parochial schools located in the United States are eligible to enter the contest.

2. Essays must be limited to 1,500 words.

3. Essays should be written on one side of letter size paper (8½ by 11 inches) and if typewritten, double spaced.

4. Each essayist must type his name, address, telephone number, school, and grade on either the cover or the first page of his essay.

5. Contest starts January 1, 1954, and essays must be submitted on or before March 1, 1954, to the county or auxiliary sponsoring the contest or to the state chairman.

6. The first three prize winning essays from each county medical society must be sent to the state chairman on or before March 15, 1954.

7. The first three prize winning essays from each state must be sent to the AAPS on or before April 1, 1954.

8. Compositions must be original and should be well documented.

9. Judging will be based solely on knowledge and grasp of the subject supported with documentation and sound logical conclusions.

10. Judges for county, state, and national contests will be a physician, an educator, and another person, all of whom shall have some special knowledge of the subject.

Small packaged libraries with bibliography may be secured free of charge by writing the AAPS, 360 North Michigan Avenue, Chicago 1.

County societies and auxiliaries are urged by Dr. Rumph to begin at once working out arrangements with school officials if they have not already done so.

Southern Medical Association

Host to the Southern Medical Association meeting in Atlanta, Ga., from October 26 to 29 will be Fulton County Medical Society.

The program plan will follow that for the Dallas and Miami meetings of the last two years, which were well received. Included will be forty-seven half-day section sessions, the general session, conjoint meetings, and exhibits. Meetings, exhibits, and registration will all be housed in the Municipal Auditorium, which is within walking distance of downtown Atlanta hotels.

At the opening meeting, which is open to the public, the president, Dr. Walter C. Jones, Miami, will speak, and there will be two other addresses. The annual dinner is scheduled for Wednesday evening, October 28. Also planned are meetings, including luncheons and dinners, of various medical school alumni and fraternity groups. A golf tournament is to be held, and the Woman's Auxiliary has arranged an attractive schedule of meetings.

A number of allied medical organizations are meeting at the same time as the Association. These include the Georgia Pediatric Society; American College of Chest Physicians, Southern Chapter; Southern Gynecological and Obstetrical Society; Southern Society of Cancer Cytology; Southern Electroencephalographic Society; and Association for Research in Ophthalmology, Southern Section.

Membership in the Southern Medical Association means that the physician need not pay a registration fee for the Atlanta meeting; the membership fee of $10 also entitles him to a subscription to the *Southern Medical Journal.*

Hotel accommodations may be made by writing the Housing Bureau, Southern Medical Association, 801 Rhodes-Haverty Building, Atlanta 3, giving hotel preference, type of accommodations desired, arrival date and hour, departure date and hour, names of occupants and their addresses. All reservations will be confirmed. Further information regarding the meeting may be obtained from Mr. C. P. Loranz, Empire Building, Birmingham 3, Ala.

Basic Sciences Examination in October

The next examination of the Texas State Board of Examiners in the Basic Sciences will be given October 16 and 17 in Austin. All arrangements should be completed one week before examination time. Details may be obtained from Mrs. Betty Ratcliff, Chief Clerk, 407 Perry-Brooks Building, Austin.

South Texas Postgraduate Assembly

The Postgraduate Medical Assembly of South Texas convened July 20-23 in Houston, with twenty out-of-state medical speakers present to discuss latest developments in the fields of medicine, surgery, and diseases of the eye, ear, nose, and throat.

Dr. Herman E. Dustin, Houston, assumed the presidency, and Dr. C. A. Dwyer, Houston, was named president-elect by approximately 2,000 doctors who attended the closing session of the assembly's nineteenth annual meeting. Other officers include Drs. Harvey Renger, Hallettsville; W. H. Pipkin, Baytown; and L. M. Ship, Henderson, vice-presidents; Dr. Edward T. Smith, Houston, secretary; Dr. Charles D. Reece, Houston, treasurer; and Dr. C. F. Jorns, Houston, new member of the executive board.

Among the speakers at luncheon meetings were Senator Everett M. Dirksen of Illinois and Dr. George Turner, El Paso, President of the Texas Medical Association.

The following distinguished guest lecturers participated in the program: Drs. Rudolf Aebli, New York; Harry E. Bacon, Philadelphia; Louis T. Byars, St. Louis; R. F. Farquharson, Toronto; John W. Harris, Madison, Wis.; Lawrence E. Hinkle, Jr., New York; Howard P. House, Los Angeles; Robert R. Kierland, Rochester, Minn.; Donald S. King, Boston; Irving Henry Leopold, Philadelphia; Howard R. Mahorner, New Orleans; Robert A. Moore, St. Louis; C. Stewart Nash, Rochester, Minn.; Don H. O'Donoghue, Oklahoma City; James L. Poppen, Boston; R. L. Sanders, Memphis; W. W. Scott, Baltimore; Walter L. Thomas, Durham, N. C.; Philip Thorek, Chicago; and Wolf W. Zuelzer, Detroit.

Motion pictures were shown and scientific and technical exhibits were on display during the assembly.

SOUTHWESTERN STUDENTS DAY

September 10 in Dallas was the first annual medical students day sponsored by the Texas Medical Association and the Dallas County Medical Society for students at Southwestern Medical School of the University of Texas.

Dr. Jack G. Kerr, president of the Dallas County Medical Society, presided, and after a welcoming address by Dr. R. W. Kimbro, Cleburne, chairman of the Association's Board of Trustees, the following talks were given: "Your Practice and Public Opinion" by Dr. Troy A. Shafer, Harlingen, chairman of the Association's Committee on Public Relations; "Legal Aspects of Your Practice" by Philip R. Overton, Austin, general counsel for the Association; "You and the Medical Society" by Dr. Charles T. Stone, Galveston, delegate of the American Medical Association's Section on Internal Medicine to the AMA House of Delegates; and "The Business Side of Your Practice" by Dr. Everett C. Fox, Dallas, immediate past chairman of the Council on Medical Economics of the Association.

Dr. Kerr moderated a question and answer period, after which a luncheon was held for senior medical students. "A Physician's Debt to Medicine," an address by Dr. George Turner, El Paso, President of the Texas Medical Association, was delivered at the luncheon.

Oklahoma City Clinical Conference

The Oklahoma City Clinical Society will hold its twenty-third annual conference October 26-29 in Oklahoma City with a postgraduate program of lectures and discussions. The program will also include round-table question and answer sessions, a clinical pathologic conference, dinner meetings, a dinner dance, and a stag smoker. All physicians who are members of their county societies may attend. Registration fee is $20.

The sixteen guest speakers follow: Dr. H. Davis Chipps, New Orleans; Dr. Edward L. Compere, Chicago; Dr. Murray M. Copeland, Washington, D. C.; Dr. Charles C. Dennie, Kansas City; Dr. William S. Fields, Houston; Dr. Erle Henriksen, Los Angeles; Dr. W. Paul Holbrook, Tucson; Dr. William G. Leaman, Jr., Philadelphia; Dr. Perry S. MacNeal, Philadelphia; Dr. Lyman Mason, Denver; Dr. George Piness, Los Angeles; Dr. Merrill J. Reeh, Portland, Ore.; Dr. Peter A. Rosi, Chicago; Dr. Francis F. Schwentker, Baltimore; Dr. Howard E. Snyder, Lawrence, Kan.; and Dr. Harry M. Spence, Dallas.

Dr. Edward J. McCormick, President of the American Medical Association, will give an address at the first banquet meeting October 26.

Further information is available from the executive secretary, 503 Medical Arts Building, Oklahoma City.

GASTROENTEROLOGICAL CONVENTION

The National Gastroenterological Association will hold its eighteenth annual convention and scientific sessions in Los Angeles October 12-14 with a program planned to include a symposium on cirrhosis of the liver and panel discussions on peptic ulcer, diseases of the large bowel, and cancer research developments. Additional papers on gastroenterology and related fields will be presented.

Following the convention on October 15-17, a postgraduate course will be given under the direction of Drs. Owen H. Wangensteen of Minneapolis and I. Snapper of Chicago. It will be the association's fifth annual course in postgraduate gastroenterology.

The convention is open to all physicians without charge; only those who have matriculated in advance may attend the postgraduate course.

Further information may be obtained by writing the executive officer of the association, 1819 Broadway, New York 23.

Southwestern Surgical Congress

The Southwestern Surgical Congress will hold its fifth annual meeting in Salt Lake City September 21-23. The following Texas physicians will participate in the scientific program: Dr. J. Peyton Barnes, Houston, "Surgical Treatment of Omphalocele"; Drs. Edgar J. Poth and Fred J. Wolma, Galveston, "The Treatment of Recurring Acute Pancreatitis by Decompression of the Biliary Tract"; Drs. G. V. Brindley, Jr. and John A. Henderson, Temple, "Mediastinal Tumors"; and Dr. John V. Goode, Dallas, councilor for Texas, who will preside over a luncheon and round-table discussion.

A general scientific program covering all phases of surgery has been planned as well as entertainment, panel discussions, and round-table discussions for members and for the ladies.

Drs. Warren H. Cole, Chicago, and Samuel F. Marshall, Boston, are to be guest speakers.

Registration fee for nonmembers only is $10. There is no registration fee for members of the Southwestern Surgical Congress or the Southeastern Surgical Congress, nor for residents, interns, military personnel, speakers, and wives.

American Association of Blood Banks

The American Association of Blood Banks will hold its sixth annual meeting October 17-20 in Chicago. Scientific programs, exhibits, and a refresher course for technologists are scheduled. Further information may be obtained from the secretary of the association, 3500 Gaston Avenue, Dallas 4.

PERSONALS

Dr. George Sladczyk, Port Arthur, was honored by local physicians with a dinner party in Port Arthur June 16 and presented with a food freezer unit, a set of cuff links and tie clasp, testimonial scroll, and honorary life membership on the St. Mary's Hospital medical staff in recognition of his many years of medical service. Dr. Sladczyk moved to Wimberley in July in semiretirement.

Dr. Joe H. McCracken, Mineral Wells, is to be honored by the University of Tennessee at its graduation exercises September 28 and awarded a certificate of merit as a tribute to his more than fifty years in medical practice.

At its recent annual meeting in Atlantic City, N. J., the Society for Pediatric Research elected *Dr. Russell J. Blattner,* Houston, vice-president.

Dr. W. C. Windham and his wife held an open house at their home in Center June 14 in observance of the doctor's fiftieth year in the practice of medicine.

Dr. W. L. Starnes, San Antonio, recently became superintendent of the San Antonio State Hospital. *Dr. Vernon Watley,* formerly of Denver, is the new director of the state hospital at Abilene.

Dr. Dick B. Gregg, Round Rock, was honored on his fifty-eighth birthday June 19 in Austin with a dinner arranged by Dr. H. D. Dollahite, administrator of the Texas Baptist Children's Home in Round Rock. Dr. Gregg was presented with a check for $1,000 for his years of service to the community.

Dr. M. A. King, Frankston, on July 8 became president of the local Lions Club. On June 26, *Dr. Robert D. Hays,* Brady, was installed as president of the Brady Lions Club for the year.

Dr. Maston L. Gray, Jacksonville, was honored by the Jacksonville Lions Club at its June 29 meeting for his outstanding work in the club auxiliary's well-baby clinic program. He was presented with a gift by the Lions and Lioness Clubs, which met jointly for the ceremony.

Dr. Andrew J. Magliolo, Dickinson, became president in July of the Nu Sigma Nu Foundation, which maintains charitable and educational undertakings at medical schools in the state.

Dr. Henry M. Winans, Jr., Dallas, was guest of honor at a buffet supper given by Mr. and Mrs. Hulen Rich July 3 in Dallas. Guests were members of the medical and administrative staffs of Baylor Hospital.

Dr. Homer Bull, brother of *Dr. John H. B. Bull,* Aransas Pass, died in his sleep June 1 in Geneseo, N. Y.

Mrs. William A. Ramey, the mother of *Dr. Paul M. Ramey,* Temple, died at her home in Sterling, Colo., June 12.

Dr. Franklin Phillip Schuster, Jr., who is interning in San Francisco, and Miss Bettie Banks Manning were married in El Paso July 3. The bridegroom's parents are *Dr. and Mrs. Frank P. Schuster,* El Paso.

POSTGRADUATE CARDIOLOGY COURSE

Cardiology and electrocardiography is the subject of a twelve-week course to be held each Monday evening, September 28-December 14, at the Texas Medical Association Memorial Library and Headquarters Building, 1801 Lamar Boulevard, Austin. Dr. Clifton D. Howe, Houston, is to be in charge of the course presented by the University of Texas Postgraduate School of Medicine in cooperation with the Texas Medical Association, the Texas State Department of Health, and the Texas Academy of General Practice. Tuition fee is $25 and twenty-four credit hours will be given.

The following speakers will take part in the program: Drs. Charles A. Armbrust, Edmond K. Doak, Sebron C Dale, E. L. Wagner, Thomas J. Fatheree, Sam I. Miller Edgar McPeak, and Howe, all from Houston.

COURSES ON CHEST DISEASES

Postgraduate courses on recent advancements in the management and treatment of heart and lung disease will be offered by the American College of Chest Physicians September 28-October 2 in Chicago and November 2-6 in New York. The courses are to be given in cooperation with respective state chapters of the college and the staffs and faculties of local hospitals and medical schools. Tuition for each course is $75.

Details are available from the executive director of the college, 112 East Chestnut Street, Chicago 11.

LIBRARY SECTION

RECENT ARTICLES BY TEXAS PHYSICIANS

Following is a continuation from the August JOURNAL of the list of articles by Texas physicians published since October, 1952, and available at the Memorial Library of the Texas Medical Association. Articles appearing in the JOURNAL are not included.

Forbes, Gilbert B.: Glycogen Storage Disease, J. Pediat. *42:*645-653 (June) 1953.

Freeman, Bromley S.: Inoculation Amebiasis Cutis, Case Report, Am. Surgeon *19:*148-154 (Feb.) 1953.

Friedewald, Vincent E.: Is Skin Testing in Allergic Patients Worth the Effort? J. Allergy *23:*420-425 (Sept.) 1952.

Friedewald, Vincent E.: Pollen Survey of West Texas, Ann. Allergy *11:*185-189 (March) 1953.

Gandy, D. Truett: Concept of Clinical Aspects of Factitial Dermatitis, South. M. J. *46:*551-555 (June) 1953.

Gill, E. King: Mycotic Infections in Otolaryngology, Laryngoscope 63:389-394 (May) 1953.

Goar, Everett L., and Smith, Louis S.: Polyarteritis Nodosa of Eye, Am. J. Ophth. *35:*1619 (Nov.) 1952.

Goode, John V., and Martin, James A.: Surgical Experience with Mammary Cancer, Growth Characteristics Observed During Treatment of 258 Private Patients with Breast Cancer, Ann. Surg. *137:*856-863 (June) 1953.

Halpert, Bela; Pollard, Claude, Jr.; and McGuire, Thomas H.: Neuroblastoma of Suprarenal Medullary Anlage with Metastasis to Brain, Cancer *6:*512-515 (May) 1953.

Hand, Albert M.: Infantile Diabetes, Diabetes *2:*85-89 (March-April) 1953.

Hartman, Albert W.; Reppert, Lawrence B.; and Smith, Roy L.: Adrenal Tumor with Cushing's Syndrome, Ann. Surg. *137:*645-651 (May) 1953.

Harvill, T. Haynes: Evaluation of Gastro-Intestinal Patient, Dallas M. J. *39:*53-59 (May) 1953.

Haynes, B. W., Jr.; Crawford, E. Stanley; Mahaffey, J. Herman; and DeBakey, Michael E.: Use of Plasma Substitutes in Treatment of Wound Shock, M. Rec. & Ann. *47:* 457-459 (March) 1953.

Hejtmancik, James H., and Childers, John H.: Clinical and Pathological Study of Carcinoma of Urinary Bladder, J. Urol. 69:377-389 (March) 1953.

Helm, Fred Power: Infant Mortality, J. Kentucky State M. A. *51:*108-110 (March) 1953.

Hendrick, James W.: Treatment of Malignancy of Buccal Mucous Membrane, Gingiva, Soft and Hard Palate, Ann. Otol., Rhin. & Laryng. *61:*1094-1113 (Dec.) 1952.

Heyer, Howard E.; Teng, H. C.; and Barris, William: Increased Frequency of Acute Myocardial Infarction During Summer Months in Warm Climate, Am. Heart J. *45:*741-748 (May) 1953.

Hoff, Hebbel E.; Breckenridge, Carlyle G.; and Spencer, William A.: Suprasegmental Integration of Cardiac Innervation, Am. J. Physiol *171:*178-188 (Oct.) 1952.

Howard, Ben K.; Goodson, James H.; and Mengert, William F.: Supine Hypotensive Syndrome in Late Pregnancy, Obst. & Gynec. *1:*371-377 (April) 1953.

Hutchins, S. P. R.: Vesical Neck Obstruction in Women, J. Urol. *69:*102 (Jan.) 1953.

Hutchins, S. P. R.: New Resectoscope, J. Urol. *69:*456-457 (March) 1953.

Irons, J. V.; Sullivan, Thelma B.; Cox, George W.; and Hale, R. A.: Outbreak of Smallpox in Lower Rio Grande Valley of Texas in 1949, Am. J. Pub. Health *43:*25-29 (Jan.) 1953.

Jackson, Ira J.: Osteoid Osteoma of Lamina and Its Treatment, Am. Surgeon *19:*17-23 (Jan.) 1953.

Jordan, George L., and Erickson, Ethel E.: Tuberculosis and Cancer of Colon, Am. Surgeon *19:*121-127 (Feb.) 1953.

Kantor, Herman I.: Treatment of Undeveloped Secretory Phase of Endometrium, Am. J. Obst. & Gynec. *65:*602 (March) 1953.

Karnaky, Karl John: Micronized Stilbestrol for Dysfunctional Uterine Bleeding and Endometriosis, South. M. J. *45:* 1166-1172 (Dec.) 1952.

Karnaky, Karl John: Diethylstilbestrol Therapy, Long Period of High Dosage Des Therapy, M. Times, New York *81:*315-317 (May) 1953.

Kelsey, John R., Jr., and Gilmore, Clarence E.: Bilateral Ductus Arteriosus Representing Persistence of Each Sixth Aortic Arch, Arch. Path. *55:*154-161 (Feb.) 1953.

Kelsey, Mavis P.: Terminal Care of Cancer Patient, South. Med. & Surg. *104:*1-5 (Jan.) 1953.

Kelsey, Mavis P.: Use of Radioiodine in Diagnosis and Treatment of Thyroid Disease, M. Rec. & Ann. *47:*485-492 (April) 1953.

Killingsworth, W. Price; McReynolds, George S.; and Harrison, A. Wilson: Pulmonary Leiomyosarcoma in Child, J. Pediat. *42:*466-470 (April) 1953.

Laurentz, Fred K.: The Key—Your Public Health Education Program, J. Texas Pub. Health A. *5:*80-82 (June) 1953.

Lavadia, P., Jr.: Retrograde Jejuno-Gastric Intussusception Am. Surgeon *19:*507-513 (June) 1953.

Letteer, C. Ralph: Endocardial Fibroelastosis, Am. Int. Med. *38:*573-582 (March) 1953.

Livesay, W. R., and Chapman, Don W.: Treatment of Acute Hypotensive States with 1-Norepinephrine, Am. J. M. Sc. *225:*159-171 (Feb.) 1953.

McCalla, Larry H.; Creech, Oscar, Jr.; and Ford, Ralph V.: Hexamethonium Ileus, Am. Surgeon *19:*115-120 (Feb.) 1953.

McConnell, Kenneth P.; Portman, O. W.; and Rigdon, R. H.: Intravascular Life Span of Duck Red Blood Cell as Determined by Radioactive Selenium, Proc. Soc. Exper. Biol. & Med. *83:*140-143 (May) 1953.

McNeill, Joseph P., and Goode, John V.: Malignant Melanoma, Am. Surgeon *19:*313-317 (April) 1953.

Miller, Sam I.; Ford, Ralph V.; and Moyer, John H.: Dibenzyline, New England J. Med. *248:*576-582 (April 2) 1953.

Mills, Lewis C., and Moyer, John H.: Treatment of Hypertension with Orally and Parenterally Administered Purified Extracts of Veratrum Viride, Arch. Int. Med. *90:*587-601 (Nov.) 1952.

Moreton, Robert D.: Roentgenologic Considerations of Gastrointestinal Lesions Causing Hematemesis, South. M. J. *46:*127-135 (Feb.) 1953.

Morris, Don P., and Soroker, Eleanor P.: Follow-Up Study of Guidance-Clinic Waiting List, Ment. Hyg. *37:*84-88 (Jan.) 1953.

Moyer, John H., and Caplovitz, Coleman: Clinical Results of Oral and Parenteral Administration of 2-(N'p-Tolyn-N'-m-Hydroxyphenylaminomethyl) Imidazoline Hydrochloride (Regitine) in Treatment of Hypertension and Evaluation of Cerebral Hemodynamic Effects, Am. Heart J. *45:*602-610 (April) 1953.

Moyer, John H.; Snyder, Harvey B.; Johnson, Ira; Mills, Lewis C.; and Miller, Sam I.: Results with Oral Hexamethonium Alone and in Combination with 1-Hydrazin-Ophthalazine (Apersoline) in Therapy of Hypertension, Am. J. M. Sc. *225:*379-398 (April) 1953.

Muirhead, E. E.; Stirman, J. A.; and Fogelman, M. J.: Cardiovascular Lesions Following Bilateral Nephrectomy of Dog, Arch. Int. Med. *91:*250-277 (Feb.) 1953.

Nau, Carl A., and Neal, Jack: Central Heating Systems and Associated Potential Dangers of Carbon Monoxide, Texas Rep. Biol. & Med. *10:*866 (Winter) 1952.

Nau, Carl A.; Neal, Jack; and Freund, A. P.: Automatic Dust Feed Apparatus Useful for Exposure of Animals to Dust Atmospheres, Texas Rep. Biol. & Med. *10:*874 (Winter) 1952.

North, John Paul, and Wollenman, Oscar J., Jr.: Venous Mesenteric Occlusion in Course of Migrating Thrombophlebitis, Surg. Gynec. & Obst. *95:*665-671 (Dec.) 1952.

O'Heeron, Michael K.; Riddel, Roy; Bozzell, James; Robinson, Jack; and Satterlee, Robert: Malignant Disease of Urinary Bladder, J. Internat. Coll. Surgeons *19:*25-42 (Jan.) 1953.

Pfeil, E. T., Jr., and Schear, E. W.: Use of Unreported Treatment in Spontaneous Pneumoventricle Following Trauma. J.A.M.A. *151:*728-730 (Feb. 28) 1953.

Pike, Robert M.; Sulkin, S. Edward; and Coggeshall, Howard C.: Serological Reactions in Rheumatoid Arthritis; Persistence of the Serum Factor Which Agglutinates Sensitized Sheep Cells, J. Lab. & Clin. Med. *41:*880-886 (June) 1953.

Portman, Oscar W.; McConnell, Kenneth P.; and Rigdon, R. H.: Blood Volumes of Ducks Using Human Serum Albumin Labeled with Radioiodine, Proc. Soc. Exper. Biol. & Med. *81:*599-601 (Dec.) 1952.

Poth, Edgar J.; Lewis, Stephen R.; and Wolma, Fred J.: Treatment of Recurring Intestinal Obstruction by Plication Procedure, Am. Surgeon *19:*24-32 (Jan.) 1953.

Rigdon, R. H.: Tumors Produced by Methylcholanthrene in Duck, Arch. Path. *54:*368-377 (Oct.) 1952.

Rigdon, R. H.; Fibroma Arising from Feather Follicle of Duck Following Local Application of Methylcholanthrene to Skin, Proc. Soc. Exper. Biol. & Med. *83:*34-36 (May) 1953.

Rigdon, R. H.; Kirchoff, Helen; and Walker, Mary Lee: Frequency of Cancer in White and Colored Races as Observed at Autopsy Between 1920 and 1949 at the Medical Branch, Texas Rep. Biol. & Med. *10:*914-928 (Winter) 1952.

Robinson, Charles: Primary Meningeal Melanomas, South. M. J. *46:*336-343 (April) 1953.

Ross, William R.: Problems in Control of Tuberculosis Patient at Home, J. Texas Pub. Health A. *5:*71-74 (June) 1953.

Shaw, Robert R.: Tracheostomy, Its Role in Postoperative and Post-Traumatic Care *19:*246-250 (March) 1953.

Smith, Howard E.: Modern Methods of Case-Finding, J. Texas Pub. Health A. *5:*68-71 (June) 1953.

Smith, Jackson A.: Methods of Treatment of Delirium Tremens, J.A.M.A. *152:*384-387 (May 30) 1953.

Smith, Jackson A.: Psychotherapy in Chronic Alcoholism, South. M. J. *46:*410-413 (May) 1953.

Smith, Jackson A., and Brown, W. T.: Treatment of Alcoholism, Am. J. Psychiat. *109:*279-282 (Oct.) 1952.

Spencer, Francis M.; Madding, Gordon F.; and Hershberger, Lloyd R.: Clinical Significance of Prolapsed Gastric Mucosa, Am. Surgeon *19:*67-77 (Jan.) 1953.

Sparkman, Robert S.: Common Fallacies Concerning Gallbladder Disease, Nebraska M. J. *37:*379-382 (Dec.) 1952.

Stevenson, Clyde A.: Roentgenologic Examination of Gallbladder Without Opacification, J.A.M.A. *151:*264-265 (Jan. 24) 1953.

Swann, H. G.; Prine, J. M.; King, B. R.; and Lowry, James S.: Intrarenal Pressure During Diuresis and Antidiuresis, J. Urol. *69:*571-577 (April) 1953.

Tucker, E. J.: Preservation of Living Bone in Plasma, Surg. Gynec. & Obst. *96:*739-749 (June) 1953.

Veirs, Everett R.: New Eresiphake Tip, Tr. Am. Acad. Ophth. *56:*934-935 (Nov.-Dec.) 1952.

Vermooten, Vincent: Management of Urinary Tract Infections, Dallas M. J. *39:*28-33 (Feb.) 1953.

White, Raleigh R.: Organic Hyperinsulinism, South. M. J. *46:*169-174 (Feb.) 1953.

Wilkins, A. N.: Urethritis in Women, GP *7:*51-53 (March) 1953.

Williams, M. J., and Clapp, M. P.: Mixed Meningitis, J.A.M.A. *151:*732-734 (Feb. 28) 1953.

Wilson, S. W.: Present Status of Adrenal Hormones, Tarrant County M. Soc. Bull. *25:*10-13 (April) 1953.

Woodson, W. Burbank: Spontaneous Unilateral Pulsating Exophthalmos, Am. J. Ophth. *36:*40-44 (Jan.) 1953.

Yates, Charles: Double Contrast Studies of Colon; Polyps in Children, South. M. J. *46:*315-319 (April) 1953.

Yow, Ellard M., and Shoemaker, Emitt H.: Influence of Antibiotics on Production and Recognition of Infections, Am. Surgeon *19:*107-114 (Feb.) 1953.

BOOKS RECEIVED IN AUGUST

Cawley, C. C.: *Fool's Haven,* Boston, House of Edinboro, 1953.

Colby, Fletcher H.: *Essential Urology,* ed. 2, Baltimore, Williams and Wilkins, 1953.

Coope, Robert: *The Quiet Art, A Doctor's Anthology,* Edinburgh, E. & S. Livingstone, 1952.

Currier, Thomas Franklin: *A Bibliography of Oliver Wendell Holmes,* New York, New York University Press, 1953.

Davis, David M.: *Mechanisms of Urologic Disease,* Philadelphia, W. B. Saunders, 1953.

Dubos, René and Jean: *The White Plague, Tuberculosis, Man and Society,* Boston, Little, Brown & Co., 1952.

Dunlop, D. M.; Davidson, L. S. P.; and McNee, Sir John: *Textbook of Medical Treatment,* ed. 6, Edinburgh, E. & S. Livingstone, 1953.

Erskin, Arthur W.: *Practical X-Ray Treatment,* ed. 4, St. Paul, Bruce Publishing Co., 1953.

Ficarra, Bernard J.: *Newer Ethical Problems in Medicine and Surgery,* Westminster, Md., Newman Press, 1951.

Gibson, H. Lou: *Copying and Duplicating Medical Subjects and Radiographs,* Springfield, Ill., Charles C. Thomas, 1953.

Glasser, Otto: *Dr. W. C. Röntgen,* Springfield, Ill., Charles C. Thomas, 1945.

Gordan, Gilbert S., and Lisser H.: *Endocrinology in Clinical Practice,* Chicago, Yearbook Publishers, 1953.

Gross, Robert E.: *The Surgery of Infancy and Childhood,* Philadelphia, W. B. Saunders, 1953.

Haessler, F. Herbert: *Ophthalmological Diagnosis,* Baltimore, Williams and Wilkins, 1953.

Kane, Irving J.: *Sectional Radiography of the Chest,* New York, Springer, 1953.

Karnosh, Louis J., and Mereness, Dorothy, *Psychiatry for Nurses,* ed. 4, St. Louis, C. V. Mosby, 1953.

Perkins, James M., and Feldman, Floyd M.: *You and Tuberculosis,* New York, Alfred A. Knopf, 1952.

Pinner, Max, and Miller, Benjamin F.: *When Doctors Are Patients,* New York, W. W. Norton, 1952.

Ross, Will: *I Wanted to Live,* Milwaukee, Wisconsin Anti-Tuberculosis Association, 1953.

Saklad, Meyer: *Inhalation Therapy and Resuscitation,* Springfield, Ill., Charles C. Thomas, 1953.

Shelley, Walter B., and Crissey, John T.: *Classics in Clinical Dermatology,* Springfield, Ill., Charles C. Thomas, 1953.

Sigerist, Henry E.: *A History of Medicine,* vol 1, *Primitive and Archaic Medicine,* New York, Oxford University Press, 1951.

Wolfe, Werner: *The Dream—Mirror of Conscience,* New York, Grune & Stratton, 1952.

Contributions to Library

Grateful acknowledgment is made by the Texas Medical Association Memorial Library of the following recent gifts:

American College of Surgeons, Chicago, 1953 Directory.

Dr. Joe W. Bailey, Austin, 2 books.

Dr. Otto Brandt, Jr., Austin, 85 unbound journals.

Dr. J. Edward Johnson, Austin, 125 journals and 43 reprints.

Dr. W. P. Morgan, Austin, 895 journals.

Mr. L. C. Scheh, Seguin, 12 journals.

Dr. N. L. Schiller, Austin, 78 journals, 2 reprints, 14 books.

Texas Tuberculosis Association, Austin, 3 books.

Dr. Samuel P. Todaro, Austin, 1 book.

MOTION PICTURES FOR LOAN

Cervical Smears in the Diagnosis of Cancer

16 mm., color, 25 minutes. (Courtesy of Dr. Karl John Karnaky, Houston.)

This is a well-executed film showing the equipment necessary in testing for cancer, together with the technique for obtaining the smear and preparing and staining the slides. The various type cancer cells as seen in the cervical smear are shown. This film is of interest to all medical groups.

Lesions of the Vulva, Vagina, and Cervix

16 mm., color, 25 minutes. (Courtesy of Dr. Karl John Karnaky, Houston.)

This film shows lesions caused by Monilia, Trichomonas, and Trichophyton and cancerous and chancroidal lesions seen by the author during the past ten years. It is of interest to general practitioners and gynecologists.

Scabies

16 mm., sound, 38 minutes. (Courtesy of British Information Services.)

Showing the methods used in diagnosis and treatment, this film includes the habits and life cycle of the mite, area of distribution of burrows under the human skin, secondary infections, and hygienic measures for eradication.

Megacolon, Total Colectomy with Ileoproctostomy for Hirschsprung's Disease

16 mm., color, 30 minutes. (Courtesy of Dr. Philip Thorek, Chicago.)

This film presents an unusual case of neglected Hirschsprung's disease in a 12 year old child who had suffered with obstipation and distention since the first year of life. It was necessary to break up a fecal impaction in the rectum which had produced a complete large bowel obstruction. The film continues to show a complete colectomy with a lateral ileoproctostomy which was performed two weeks later.

The Warning Shadow

16 mm., sound, color, 17 minutes. (Courtesy of the Texas Cancer Coordinating Council.)

This film gives a brief history of cancer of the lung. The film narration relates that in 1833 the first operation for the complete removal of a cancerous lung was performed. The patient, a pediatrician, and the surgeon, a noted chest expert, make an appearance in the film after their story has been told. They appeal for increased awareness of lung cancer in all persons past 45 years of age. This film is of interest to all lay groups, especially businessmen's and civic clubs.

BOOK NOTICES

[1]The Basis of Clinical Neurology

SAMUEL BROCK, M. D., *Professor of Neurology, College of Medicine, New York University. Third edition, 510 pages. $7. Baltimore, Williams and Wilkins, 1953.*

A comparison of the third edition with the previous editions shows that about one-half of the chapters have been rewritten and enlarged. The subject of spinal shock has been greatly expanded; discussions of optic pathways, spasticity, and herniation of the brain have been elaborated. The section on aphasia has been greatly improved and an excellent discussion of phantom limb added. Little change has been made in the basic subject matter in neurology. The illustrations have been changed only slightly.

This book contains a remarkable amount of information that would be of value to intermediate students of neurology. Discussions related to the neurologic examination and adequate discriptions of reflexes are for the most part absent. For this reason the book would leave much to be desired by a beginner in neurology. On the other hand, the discussions are not entirely adequate for advanced students.

One experiences considerable disappointment in finding that practical information as to diagnosis and therapy of even the common neurologic disorders is missing. For this reason it would have little value as a reference work for those who are not specialized in the field.

Basically, the book is a combined neuroanatomy and neurophysiology. It contains chapters on the peripheral nerves, spinal cord, brain stem, cerebellum, diencephalon, brain, vascular supply of the brain, vegetative nervous system, postural control, and cerebrospinal fluid. The last two chapters are all new and contain information on cerebral angiography (primarily the normal state) and electromyography. Adequate current bibliographies are given throughout.

The format of the book is excellent. The printing, illustrations, and paper are of the highest quality.

[1]*Ludlow M. Pence, M. D., Dallas.*

[2]Analgesia and Anesthesia in Obstetrics

J. P. GREENHILL, M. D., *Professor of Gynecology, Cook County Graduate School of Medicine; Attending Gynecologist, Cook County Hospital; Attending Obstetrician and Gynecologist, Michael Reese Hospital, Chicago. A Monograph in American Lectures in Gynecology and Obstetrics. Edited by* E. C. HAMBLEN, M. D. *$2.75. Springfield, Ill., Charles C. Thomas, 1952.*

Because of injudicious use or an erroneous choice, a significant number of babies and mothers die every year as a result of pain-relieving drugs which involve complications extending far beyond the usual problems of anesthesia. Consideration should be given to the effect on the child, the mother, and especially on the labor mechanism. Anesthetic agents are evaluated categorically: (1) those given by the hypodermic, oral, or rectal route, (2) inhalation agents, (3) intravenous anesthesia, and (4) block anesthesia.

Asphyxia is the chief hazard for the child as drug depression, independent of anoxemia, is of limited duration whereas oxygen want may be fatal. The author is opposed to "twilight sleep" because of restlessness necessitating restraint, difficulty of asepsis, increased operative delivery, and the increase neonatal mortality due to the cumulative effect on the child. Some will disagree with the statement that Demerol given intravenously produces a "sudden fall in blood pressure." Trilene offers no advantage over other drugs for actual anesthesia. Aspiration of vomitus contributed to about 100 deaths annually. Details with illustrations are given for the administration of caudal and spinal anesthesia although the author cautions that the latter is the most dangerous type for pregnant women.

Dr. Greenhill's preference for direct infiltration and pudendal block anesthesia is well known. The physician must be "convinced that local is the safest and simplest of all anesthesia." He must learn the technique and be willing to sacrifice the extra time and effort demanded. Sixteen advantages of local pudendal block anesthesia are listed, not mentioning that 100 per cent oxygen can be given simultaneously. Reed's method and hypnosis are briefly described.

This compact source of ready information is highly recommended for anyone delivering babies, especially the busy practitioner whose study time is limited.

[3]A Vitamin Digest

GUY W. CLARK, *Technical Director, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y. $6.50. Springfield, Ill., Charles C. Thomas, 1953.*

The author has gone into minute detail to cover fully the vitamin field. He has prepared a complete review of the extensive research dealing with this important phase of therapeutics. The chemical formulas, animal experimentations, dietary effects, and the proven human medicinal values have been covered in such a manner as to present the facts from which the reader can form his own evaluation of each vitamin and allied compounds.

The author has reduced to a small volume the pertinent information desired by many physicians. The digest is of particular value to those physicians who began practicing in the ante-vitamin days before this field of therapeutics had become a part of the school curriculum. Many physicians have had difficulty in unraveling the maze of information to the point that it could be properly incorporated in his therapeutic armamentarium. Much of the

[2]*J. C. Dunlap, M. D., Waco.*
[3]*J. A. Hockaday, M. D., Port Isabel.*

information in the digest is of recent origin and is of like value to the graduates of later years.

The author's comments and conclusions regarding the metabolic processes of the ingested vitamins both in the natural state and in the synthetic form, the co-relationship of one vitamin to another, the bacterial and intestinal synthesis, the effects of present day food processing upon vitamins in our daily diet, and the effect of vitamins on physiologic processes make of his digest a superb but brief and practical presentation of the subject.

[1]Functional Endocrinology—From Birth Through Adolescence

NATHAN B. TALBOT, M. D., *Associate Professor of Pediatrics, Harvard University;* EDNA H. SOBEL, M. D., *Instructor in Pediatrics, University of Cincinnati College of Medicine;* JANET W. MCARTHUR, M. D., *Instructor in Gynecology, Harvard University; and* JOHN D. CRAWFORD, M. D., *Instructor in Pediatrics, Harvard University. $10. Cambridge, Mass. Published for the Commonwealth Fund, Harvard University Press, 1952.*

So striking are the clinical disorders arising from gross disturbances of the endocrine glands that endocrinology has come to mean for many physicians a subject concerned with bizarre aberrations of bodily structure and function. The fat boy with small genitalia, the bearded woman, the child with the grossly deformed skeleton—such disorders are too often labeled endocrinopathies to be treated with hormones or promptly dispatched to a specialist. On the other hand, the crucial role of the endocrine glands as regulatory mechanisms for the control of normal physiologic processes is often overlooked. As a consequence, endocrinology tends to be segregated from the rest of internal medicine into a specialized compartment dealing with bizarre and rare disorders about which there is great mystery.

This book is an excellent corrective. Each chapter, which is devoted to a single endocrine gland, starts with a clear elucidation of the physiologic effects of glandular activity. On the basis of this physiologic information, the rationale and reliability of various practical diagnostic tests are explained and interpreted. Finally, within this framework of normal physiologic function, two types of clinical disorders are analyzed in the concluding sections of each chapter: (1) those alterations in endocrine activity unassociated with endocrine diseases, representing a normal adaptive response to various stresses, and (2) alterations in endocrine functions which constitute primary disease of the endocrine glands.

The discussion is well informed, carefully critical, judicious. Physiologic information is balanced with excellent clinical analyses. The net effect is a movement away from a consideration of disconnected syndromes and presentation, so far as present knowledge permits, of endocrine disorders as instances of disturbed physiology. The approach eschews the role of mystery and substitutes in its stead hard empirical data and careful generalizations. The lucid style and excellent diagrams make for pleasant as well as informative reading.

[1]*Donald W. Seldin, M. D., Dallas.*

[2]B-Vitamins for Blood Formation

THOMAS H. JUKES, Ph. D., *Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y. Edited by* CHAUNCEY D. LEAKE, Ph. D., *Vice-President in Charge of Medical Affairs, The University of Texas Medical Branch, Galveston. A Monograph in American Lectures in Pharmacology. 113 pages. $4. Springfield, Ill., Charles C. Thomas, 1952.*

This short monograph is a review of the chemistry and physiology of pteroylglutamic acid and its chemical relatives; the vitamin B_{12} group, and the "intrinsic factor." The book is highly technical but definitely stimulating. It combines brief historical notes, factual data on the sources and manufacture of the vitamins with careful descriptions of their physical and chemical properties, and thought-producing discussions of the biologic actions and interactions of the vitamins. It closes with a short chapter on vitamin B_{12} deficiency in relation to anemia.

[2]*Caroline Crowell, M. D., Austin.*

ORGANIZATION SECTION

COUNTY SOCIETIES

Lubbock-Crosby Counties Society

August 4, 1953

(Reported by Frank C. Goodwin, Secretary)

Surgery of Mitral Valve—John Selby, Lubbock.
Discussion—William H. Gordon, Orville B. Hull, and Roy Sheffield, Lubbock.

At the regular monthly meeting of the Lubbock-Crosby Counties Medical Society held in Lubbock August 4, a committee was appointed to be responsible for the success of a series of television broadcasts to be presented in the form of a panel of physicians who would answer questions sent in by the audience. William H. Gordon was named chairman, to be assisted by O. W. English, Frank B. Malone, and J. D. Donaldson, Jr. The broadcast series had been proposed by station KCBD-TV as a public service feature.

Dr. Donaldson reported for the public relations committee, and Allen T. Stewart discussed the Naturopathic Act and the new autopsy law. Wallace I. Hess, president, presided over the meeting.

The above scientific program was presented by Dr. Selby and illustrated by lantern slides and a color film.

Medina-Uvalde-Maverick-Val Verde-Edwards-Real-Kinney-Terrell-Zavala Counties Society

June 12, 1953

Trauma of Eye—Elizabeth Donaldson, Del Rio.
Jaundice—Bucky L. Burditt, Del Rio.
Acute Cholecystitis—Dean P. Dimmitt, Uvalde.
Three Interesting Cases—Cary Poindexter, Crystal City.

Approximately fifteen doctors and their wives attended the joint dinner-meeting of the Medina-Uvalde-Maverick-Val Verde-Edwards-Real-Kinney-Terrell-Zavala Counties Medical Society and its woman's auxiliary June 12 in Del Rio, following the society's scientific program, which was presented as outlined above.

Dr. Burditt, society president, presided.

Milam County Society

June 25, 1953

A conducted tour through the Alcoa plant at Rockdale June 25 preceded the program of the Milam County Medical Society, meeting with the County Nurses Association, the Woman's Auxiliary to the Milam County Medical Society, and visiting physicians from Taylor and Giddings. After a discussion of industrial medicine, the group had dinner in the plant cafeteria.

DISTRICT SOCIETIES

Fifth and Sixth Districts Society

July 10-11, 1953

(Reported by Robert J. Sigler, Secretary)

Tumors of Neck—Cornelius E. Sedgwick, Boston.
L. E. Cell Phenomenon—Malcolm M. Hargraves, Rochester, Minn.
Virus Diseases in Children—Russell J. Blattner, Houston.
Role of Doctor in Underwriting of Substandard Cases—W. H. Scoins, Fort Wayne, Ind.
Carcinoma of Cervix—Clarification of Present Knowledge—William R. Guerriero, Dallas.
Systemic Lupus Erythematosus—Dr. Hargraves.
Reticulo-Endotheliosis—Dr. Blattner.
Indications for Surgery in Treatment of Ulcerative Colitis—Dr. Sedgwick.
Complications of Diverticulitis Requiring Surgery—Dr. Sedgwick.
Carcinoma of Fundus of Uterus and Ovaries—Clarification of Present Knowledge—Dr. Guerriero.

The above scientific program was presented during the annual meeting of the Fifth and Sixth Districts Medical Society July 10-11 in Corpus Christi. An address of welcome was given by M. C. Kendrick, Corpus Christi, president of the Nueces County Medical Society, with a response by Y. C. Smith, Corpus Christi, district president. George Turner, El Paso, President of the State Association, addressed the group. Panel and round-table discussions were held as were a luncheon and an open house and dinner dance. Such recreation as a golf tournament, fishing, motor boating, sailing, and sight-seeing were also on the agenda.

The following new officers were elected at the business meeting; O. S. Koepsel, Corpus Christi, president; Amos Graves, San Antonio, vice-president; and E. Jackson Giles, Corpus Christi, secretary-treasurer.

Approximately 200 doctors from the two districts attended.

Thirteenth District Society

June 17, 1953

(Reported by Robert D. Moreton, Secretary)

Symposium: Hemoptysis—Knox Pittard, Anson, Moderator.
Internist—Wayne A. Reser, Wichita Falls.
Radiologist—David H. Allen, Wichita Falls.
General Practitioner—John C. Allensworth, Mineral Wells.
Pathologist—Jarrett E. Williams, Abilene.
Otolaryngologist—J. D. Magee, Abilene.
Cardiologist—Stephen W. Wilson, Fort Worth.
Thoracic Surgeon—James O. McBride, Fort Worth.

Panel Discussion: Doctor-Patient Relationship. The Socioeconomic Side—Robert W. Kimbro, Cleburne, Moderator.
Tips on Office Organization—Mr. W. E. Syers, Austin.
Legal Aspects of Your Practice—Mr. Philip R. Overton, Austin.
Is There a Doctor Shortage?—Chester U. Callan, Rotan.
Public Relations at the County Society Level—Clinton E. Adams, Abilene.

Socioeconomic Problems Facing American Medicine—F. J. L. Blasingame, Wharton.

Sixty-three members of the Thirteenth District Medical Society attended the group's annual meeting June 17 in Wichita Falls. The above program was presented, and new officers were elected. They are William E. Crump, Wichita Falls, president; Mal Rumph, Fort Worth, vice-president; and Robert D. Moreton, Fort Worth, secretary.

The following state officers were introduced by R. E. L. Gowan, Graham, president of District 13: Robert W. Kimbro, chairman of the Board of Trustees; T. H. Thomason, Treasurer; H. O. Deaton, Speaker of the House of Delegates; and May Owen, chairman of the Council on Scientific Work. Dr. Rumph spoke on the Association of American Physicians and Surgeons essay contest of which he is national chairman. R. G. Baker, Fort Worth, Councilor, gave a report and introduced F. J. L. Blasingame, Wharton, President-Elect of the Association, who addressed the group.

The 1954 meeting is to be held in Fort Worth, the date to be announced later.

AUXILIARY SECTION

SOUTHERN AUXILIARY CONVENTION

The Woman's Auxiliary to the Southern Medical Association will meet October 26-29 in Atlanta, Ga., with Mrs. Richard F. Stover, Miami, Fla., President, presiding. Business sessions will be held Tuesday and Wednesday mornings, October 27-28. Mrs. Leo J. Schaefer, Salina, Kan., President of the AMA Auxiliary, will be a guest speaker.

Tentative arrangements include a luncheon or tea Tuesday at which time Dr. Frank G. Slaughter, surgeon and novelist, will be guest speaker. Two southern doctors of the year will be honored at a Doctor's Day Luncheon Wednesday. They are Drs. William L. Pressly, Due West, S. C., and J. M. Travis, Jacksonville, Texas.

Mrs. Stanley A. Hill, Corinth, Miss., will be installed as President at the Wednesday morning meeting.

Officers of the Woman's Auxiliary to the Texas Medical Association: President, Mrs. E. W. Coyle, San Antonio; President-Elect, Mrs. Mark H. Latimer, Houston; First Vice-President (Organization), Mrs. John D. Gleckler, Denison; Second Vice-President (Physical Examinations), Mrs. Cecil O. Patterson, Dallas; Third Vice-Presidents (Today's Health), Mrs. Ralph B. Payne, Amarillo; Fourth Vice-President (Program), Mrs. Guy Knolle, Houston; Recording Secretary, Mrs. Paul Brindley, Galveston; Corresponding Secretary, Mrs. Charles L. McGehee, San Antonio; Treasurer, Mrs. Oscar M. Marchman, Jr., Dallas; Publicity Secretary, Mrs. Allen H. Neighbors, Jr., Austin; Parliamentarian, Mrs. H. S. Renshaw, Fort Worth.

COUNTY AUXILIARIES

Brazoria County Auxiliary

Twelve members of the Woman's Auxiliary to the Brazoria County Medical Society were present May 28 in Freeport when Dr. Robert Hale, county health director, spoke on health standards in the county. He was introduced by Mrs. Robert C. Miller, Lake Jackson, president. Following his talk, Mrs. M. P. Woolf, Freeport, a new member, was welcomed.

The date for the auxiliary's dance was set for February 13 in Freeport.

Upon motion by Mrs. R. M. McCary, Freeport, the group voted to send another girl to nursing school. Mesdames A. O. McCary, Freeport; B. H. Carlton, Freeport; and William C. Holt, Angleton, were appointed to pass on applicants.

It was decided that extra copies of the yearbook be provided for new members and for the State Auxiliary.—Mrs. W. D. Nicholson, Recording Secretary.

Cherokee County Auxiliary

The annual installation meeting of the Cherokee County Woman's Auxiliary was held May 5 in the home of Dr. and Mrs. T. H. Cobble, Rusk. New officers follow: Mesdames Collier Rucker, Jacksonville, president; R. T. Travis, Jacksonville, vice-president; Hugh F. Rives, Jacksonville, corresponding secretary-treasurer; C. L. Jackson, Rusk, recording secretary; and M. J. Kuykendall and Joe D. Crawford, both of Jacksonville, reporters.

Mrs. Jackson was in charge of the installation. Eighteen auxiliary members attended.

Ellis County Auxiliary

The Woman's Auxiliary to the Ellis County Medical Society honored the doctors of the community with a dinner in Ennis in May. Mrs. B. C. Wallace, Jr., Waxahachie, president, presided.

Approximately forty guests from Waxahachie, Ennis, and Ferris attended.

Jefferson County Auxiliary

The Port Arthur and Beaumont chapters of the Woman's Auxiliary to the Jefferson County Medical Society held a joint meeting and installation of officers May 12 in Beaumont to close the year's activities.

New officers, all of whom are from Port Arthur, follow: Mrs. D. S. Curry, president; Mrs. Price Killingsworth, president-elect; Mrs. Gordon Healey, first vice-president; Mrs. James M. Loewenstein, second vice-president; Mrs. J. M. White, Jr., secretary; Mrs. L. R. Byrd, Jr., treasurer; Mrs. F. J. Beyt, parliamentarian; and Mrs. E. C. McRee, historian.

Inducting officer was Mrs. W. G. Wallace, Beaumont, and hostess chairman was Mrs. R. T. Lombardo, Beaumont. Assisting with the hostess duties were Mesdames Richard Barr, J. Q. Blackwood, Julian Fertitta, J. A. Bybee, T. C. Mitchell, P. H. McNemer, and W. J. Gray, all of Beaumont.

Nueces County Auxiliary

The May meeting of the Nueces County Auxiliary was a luncheon in Corpus Christi with Mrs. W. L. Crowdus, secretary of the local chapter of the American Cancer Society, as guest speaker. Hostesses were Mesdames Hugh Kennedy, E. A. Danford, G. W. Edgerton, Sanford Glanz, Jack F. McKemie, George O'Byrne, C. P. Jimenez, Philip P. Rosenheim, and H. B. Woods.

Dr. and Mrs. J. I. Tyree were hosts June 6 in Corpus Christi for the annual picnic of the Nueces County Auxiliary. Serving as hostesses were Mesdames James L. Barnard, J. G. Bryson, J. E. Gardner, L. W. O. Janssen, C. R. Little, D. C. Steward, L. D. Wright, June Yates, and Thomas L. York.—Mrs. William E. Morris, Reporter.

Wichita County Auxiliary

A coke party May 12 at the home of Mrs. George Seibold, Wichita Falls, climaxed the meetings for the season of the Woman's Auxiliary to the Wichita County Medical Society. Hostesses were Mesdames Claude Wilson, J. H. Acker, Joe Steed, William L. Rector, H. P. Ledford, L. D. Parnell, T. Roger Humphrey, J. D. Hall, O. T. Kimbrough, W. B. Whiting, and Bailey Collins.

DISTRICT AUXILIARIES

Fifth and Sixth Districts Auxiliary

A luncheon and style show was featured at the July 10-11 meeting in Corpus Christi of the Woman's Auxiliary to the Fifth and Sixth Districts Medical Society. Mrs. Sam Powell, president of the Nueces County Woman's Auxiliary, presided at the luncheon; Mrs. June Yates, Council Woman for District 6, presided at the business meeting. A special guest was Mrs. E. W. Coyle, San Antonio, President of the State Woman's Auxiliary.

Co-chairmen of arrangements for the luncheon were Mrs. Harold Griffin and Mrs. W. E. Riley, assisted by Mesdames William Horbaly, A. K. Rodholm, Y. S. Jenkins, and A. F. Tasch.

Mrs. F. F. Rogers and Mrs. J. R. Riley served as co-chairmen in charge of the style show. Others on the committee were Mesdames J. G. Bryson, E. King Gill, O. S. Koepsel, and H. Gordon Heaney.

Models for the style show included Mesdames Damon Bernwanger, Bryson, Chalmer D. Dixon, L. P. Guttman, Alfred L. Lane, C. R. Little, William E. Morris, J. R. Riley, George Schuster, C. B. Slabaugh, Tasch, and James I. Tyree.

Also on the July 10 program was a cocktail party and dinner dance for doctors and their wives.

All the above mentioned women are from Corpus Christi except for Mesdames Tasch and Jenkins, who are from Taft.

DEATHS

W. W. NESBIT

Dr. William W. Nesbit, who was the medical officer in charge of the United States Marine Hospital in Galveston from April, 1946, to June, 1949, died of a heart disease May 7, 1953, in Seattle, Wash.

Dr. Nesbit was born in Roxbury, Pa., March 26, 1902, and received his education at schools in Chambersburg, Pa.; at Dickinson College, Carlisle, Pa.; and at Jefferson Medical College of Philadelphia, from which he was graduated with a medical degree in 1926. He then became a commissioned medical officer in the United States Public Health Service; and after a rotating internship at the Norfolk Marine Hospital, he served as chief of medical service at the Detroit Marine Hospital, assistant chief of the hospital division of the United States Public Health Service, senior medical officer of the United States Coast Guard Academy, member of the medical staff at the headquarters of Admiral Chester W. Nimitz, and medical officer in charge of the United States Public Health Service Hospitals in Galveston, New Orleans, and Seattle. Dr. Nesbit was with the Galveston hospital during the Texas City disaster.

Dr. Nesbit belonged to the American Medical Association and the Texas Medical Association through the Galveston County Medical Society.

While in Galveston, he was prominent in Red Cross work and was chairman of Armed Forces Day observances.

His wife survives him, as do a son, William D. Nesbit, Seattle, Wash., and two daughters, Mrs. Nancy A. Capo and Miss Jean V. Nesbit, both of New Orleans.

An obituary ordinarily will not be published more than four months after date of death. Cooperation in reporting deaths of physicians and in furnishing appropriate biographical material promptly is solicited.

J. R. DALE

Dr. John Richard Dale, Diboll, Texas, died May 18, 1953, in a Houston hospital of heart failure.

Dr. Dale was born December 1, 1886, in Arkadelphia, Ark., the son of Dr. John Richard Dale and May (Beauchamp) Dale. He received his education at Washington and Lee University in Lexington, Va.; a military academy in the Old South; and the University of Virginia Department of Medicine, Charlottesville, Va. He also studied one summer at the University of Chicago School of Medicine, Chicago. After Dr. Dale received his medical degree in 1915, he practiced in Diboll and Corrigan, Texas, and in Fordyce and Texarkana, Ark. He served as a lieutenant in the United States Army Medical Corps during World War I. Industrial practice was his specialty.

A member of the American Medical Association and the Texas Medical Association through the Angelina County Medical Society, of which Dr. Dale was president in 1946, Dr. Dale also had belonged to the Polk-San Jacinto Counties Medical Society. He was a member of the Presbyterian Church, the Masonic Lodge, Knights Templar, Scottish Rite, Elks, and Oddfellows.

On May 11, 1920, Dr. Dale married Miss Alice Lucile Ashford in Lufkin. His wife, who resides in Diboll, survives him, as do a son, John Richard Dale, III, Lufkin, and a sister, Miss Christine Dale, Texarkana, Ark.

J. R. WORLEY

Dr. John Reeves Worley, Dallas, Texas, died in a Dallas hospital June 26, 1953.

Dr. Worley was born in Osawatomie, Kan., June 22, 1879, and attended Kansas University and the University Medical College of Kansas City, from which he received his medical degree May 1, 1909. His specialty was urology, dermatology, and anesthesia. Dr. Worley had been practicing in Dallas since 1913 and had been professor of anesthesia at Baylor University College of Medicine when it was in Dallas.

A member of the American Medical Association and the Texas Medical Association through the Dallas County Medical Society, Dr. Worley was a thirty-second degree Mason and a Shriner.

Survivors include two sons, John R. Worley, Jr., Benton City, Wash., and G. R. Worley, LaPorte, Texas; two daughters, Mrs. J. W. McClain, Alton, Ill., and Mrs. Margot Palmer, Los Angeles; and ten grandchildren.

E. K. ARMISTEAD

Dr. Ernest King Armistead, El Paso, Texas, died May 28, 1953, of cardiac arrest in an El Paso hospital after being in a coma since an operation April 30.

Born in Campbell, Ala., June 8, 1884, the son of Robert and Maria Ann Armistead, Dr. Armistead attended schools in Alabama before entering Maryland Medical College, Baltimore, from which he received his medical degree in 1911. He interned at Macon Hospital in Macon, Ga., and practiced in Albany, Ga., for three years before moving to El Paso, where he lived until his death. While in El Paso, Dr. Armistead served for a time with the United States Public Health Service. He was a veteran of World War I and a surgeon.

A member of the American Medical Association and the Texas Medical Association through the El Paso County Medical Society for many years, Dr. Armistead also belonged to the Southern Medical Association and the Southwestern Medical Association. He was a thirty-second degree Mason, a member of the Shrine, and a member of the Methodist Church.

Dr. Armistead married Miss Edna Oliver July 3, 1915, in Macon, Ga. Survivors include a daughter, Mrs. Mary Esther Evans, Atlanta, Ga.; a sister, Mrs. Edna Kittinger, Rumsey, Ky.; and a brother, Dr. S. D. Armistead, Robertsdale, Ala.

W. T. WEBB

Dr. William Thomas Webb, Breckenridge, Texas, died in that city May 29, 1953, of bronchopneumonia.

Born November 4, 1873 at Sheltonville, Ga., Dr. Webb was the son of Mr. and Mrs. C. W. Webb. The family moved in 1889 to Texas, where Dr. Webb attended common schools. He was graduated from the Physio-Medical College of Texas, Dallas, in 1906 and practiced at Necessity for two years, Graham for two years, Haskell for one year, and Megargel for six years. In 1919 he moved to Breckenridge, where he practiced until a few months before his death. There he was county health officer for seven years and city health officer for several terms.

Dr. Webb was a member of the American Medical Association and the Texas Medical Association through the Eastland-Callahan-Stephens-Shackelford-Throckmorton Counties Medical Society, of which he was president in 1935 and in 1942. He was a member of the Masonic Lodge and the Baptist Church.

DR. WILLIAM T. WEBB

Dr. Webb married Miss Maggie Pierce in 1905; she died in 1923. Surviving Dr. Webb are a son, W. E. Webb, Atlanta, Ga.; a daughter, Mrs. James B. Duvall, Breckenridge; a brother, S. W. Webb, Prescott, Ariz.; his stepmother, Mrs. Lula Webb, Mineral Wells; and three grandchildren.

N. C. ANDRONIS

Dr. Nicholas C. Andronis, Galveston, Texas, died of cancer May 19, 1953, in a Houston hospital.

Dr. Andronis was born at the Island of Thassos, Greece, January 23, 1891, the son of Constantine and Mary Andronis, and came to the United States when he was twelve years old. He studied at schools in New York and Massachusetts, including Springfield Academy at Springfield, Mass., and was graduated from Bates College in Maine before entering the University of Texas Medical Branch, Galveston, from which he received his medical degree in 1918. Dr. Andronis interned at the John Sealy Hospital in Galveston and was adjunct professor of surgery at the Medical Branch in Galveston from 1920 to 1932 and an attending specialist with the United States Marine Hospital in Galveston from 1920 to 1949. He had been practicing in Galveston until his illness.

At the 1953 annual session of the Texas Medical Association in Houston, Dr. Andronis was elected to inactive membership. He belonged to the American Medical Association, the Eighth District Medical Society, and the Galveston County Medical Society, which he once served as secretary, as well as the American Surgical Hygiene Association and the Association of Military Surgeons. Dr. Andronis was a member of Phi Beta Kappa honorary fraternity, Theta Kappa Psi medical fraternity, the Masonic Order, the Ameri-

can Legion, the Elks Club, the Lions Club, the Knights of Pythias, and the Greek Orthodox Church. He was the author of "Fundamentals of the English Language."

Surviving Dr. Andronis are his mother, Mrs. Mary Andronis; a sister, Miss Calliopi Andronis; and a brother Ulisses Andronis; all of the Island of Thassos, Greece. Also, a brother, Dr. A. Andronis, of Galveston, and two nieces of Galveston survive.

W. THOMAS

Dr. William Thomas, Terrell, Texas, died at his home June 30, 1953, of general debility associated with arthritis.

Born in Friendship, Texas, April 15, 1882, the son of W. G. and Sallie (Kimbrough) Thomas, Dr. Thomas received his medical degree from the University of Nashville Medical Department in 1905 and did postgraduate training in psychiatry at Tulane University School of Medicine, New Orleans. He then spent five years at Matador, six years at Terrell, ten years with the United States Public Health and Veterans Bureau, ten years as superintendent of the Rusk State Hospital, ten years as superintendent of the Terrell State Hospital, and three years as superintendent of the Mexia State School until 1950, when he retired. During World War I he served in the United States Army Medical Corps. He was many times an expert witness in sanity trials.

A member almost continuously since 1906 and an honorary member since 1951 of the Texas Medical Association

DR. WILLIAM THOMAS

through the Kaufman County Medical Society, Dr. Thomas also belonged to the American Medical Association, the Masonic Lodge and Shrine, and the Baptist Church; had served as president of the Terrell Chamber of Commerce, the Cherokee County Medical Society, the Rusk Kiwanis Club, and the Terrell Rotary Club; and was an officer of the Texas Fox Hunters' Association at one time. He taught a men's Bible class for many years.

Dr. Thomas married Miss Carrie Samford October 5, 1906, in Wills Point. She survives as do the following: a son, Dr. L. S. Thomas, Dallas; four brothers, Truman Thomas of St. Jo, Ark., Horace Thomas of Dallas, and M. K. Thomas and Pleas Thomas, both of Wills Point; a sister, Mrs. A. J. Tyler, Dallas; and two grandchildren.

C. M. WILLIAMSON

Dr. Cleburne M. Williamson, Corpus Christi, Texas, died at his home May 24, 1953, of a cerebral hemorrhage.

Born in Belmont October 17, 1893, the son of Dr. and Mrs. Cleburne Williamson, Dr. Williamson attended Seguin High School, Southern Methodist University at Dallas, and Southwestern University at Georgetown before receiving his medical degree from the University of Texas School of Medicine, Galveston, in 1923. After interning at the Robert B. Green Hospital, San Antonio, he practiced in San Antonio, Donna, and Edinburg before entering civil service work for the United States Government. In 1935 while he was in Edinburg, Dr. Williamson was superintendent and chief of staff of the City-County Hospital. He settled in Corpus Christi in 1943 after practicing in Eagle Pass for a short time. His specialty was gynecology and surgery.

Dr. Williamson was a member of the American Medical Association and the Texas Medical Association through the Nueces County Medical Society. He had been a member also of the Medina-Uvalde-Maverick-Val Verde-Edwards-Real-Kinney-Terrell-Zavala Counties Medical Society and the Hidalgo County Medical Society, of which he was president in 1933. He was a veteran of World War I and a member of Phi Rho Sigma medical fraternity.

Survivors include his wife, Mrs. Elizabeth Williamson; his father, Dr. C. Williamson, San Antonio; and a sister, Mrs. Paul McSween, San Antonio.

A. H. BRADEN, SR.

Dr. Albert H. Braden, Sr., Houston, Texas, died of cancer July 22, 1953, in that city.

Born October 30, 1886, in Bernardo, Texas, Dr. Braden attended schools there and in Austin and also was graduated from the University of Texas School of Medicine, Galveston, in 1913. After an internship in the Hotel Dieu in Beaumont, he practiced in Beaumont, Waco, and Sherman, before settling in 1922 in Houston, where he specialized in allergy until his death. Dr. Braden, who had been a pathologist at St. Joseph's Hospital, Houston, for many years, was an honorary member and former president of the staff of St. Joseph's. He was on the teaching staff in pathology and bacteriology of St. Joseph's School of Nursing and of the Sacred Heart College, both in Houston. Dr. Braden, who was certified by the American Board of Pathology, was an advisory editor of the *American Journal of Medical Technology*.

A member of the American Medical Association and the Texas Medical Association through the Harris County Medical Society, Dr. Braden also belonged to the American College of Allergists, American Academy of Allergy, International Correspondence Society of Allergists, American Society of Clinical Pathologists, American Association for the Advancement of Science, Southern Medical Association, Southwest Allergy Forum, Texas Society of Pathologists, and the Postgraduate Medical Assembly of South Texas. He also was affiliated with Alpha Kappa Kappa medical fraternity and a member of the Catholic Church. Dr. Braden served as secretary of the Jefferson County Medical Society in 1916-1917, secretary of the District 10 Medical Society in 1917, secretary of the Section on Pathology for the 1930 annual session of the Texas Medical Association, and president in 1944-1945 of the Texas Society of Pathologists.

Dr. Braden married Miss Kathleen O'Connor in Temple in 1915. She survives him. Other survivors include four sons, Dr. Albert H. Braden, Jr., and the Rev. Patrick Braden, C. S. B., both of Houston, Dr. David Braden, Galveston, and J. C. Braden, Austin; and one daughter, Mrs. Kathleen Eichelberger, Fairbanks, Alaska.